

MCFEE, ELVIS C. M.S. Protodecarboxylation of β -Keto-Acrylates and Synthesis of Isomaleimides By Dehydration of Maleamic Acids Using Methanesulfonyl Chloride. (2021)

Directed by Dr. Mitchell Croatt. 125 pp.

Abstract: The development of unique reaction conditions for the protodecarboxylation of β -keto acrylic acids is described. This expansion on previous work ameliorates the requirement of added water, affording a homogeneous reaction system. As an unexpected discovery in substrate preparation, the synthesis of isomaleimides using methanesulfonyl chloride as a dehydrating agent is also presented.

PROTODECARBOXYLATION OF B-KETO-ACRYLATES AND SYNTHESIS OF
ISOMALEIMIDES BY DEHYDRATION OF MALEAMIC ACIDS USING
METHANESULFONYL CHLORIDE

by

Elvis C. McFee

A Thesis Submitted to
the Faculty of The Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Greensboro

2021

Approved by

Committee Chair

DEDICATION

To Jesse, Angel, and Rebecca.

APPROVAL PAGE

This thesis written by Elvis McFee has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair Dr. Mitchell P. Croatt

Committee Members Dr. Kimberly Peterson

Dr. Jonathan R. Chekan

Date of Acceptance by Committee

Date of Final Oral Examination

TABLE OF CONTENTS

DEDICATION	ii
APPROVAL PAGE	iii
LIST OF TABLES	v
LIST OF SCHEMES	vi
CHAPTER I: INTRODUCTION	1
CHAPTER II: PROTODECARBOXYLATION OF B-KETO ACRYLIC ACIDS	5
CHAPTER III: SYNTHESIS OF ISOMALEIMIDES BY DEHYDRATION OF MALEAMIC ACIDS USING METHANESULFONYL CHLORIDE	18
CHAPTER IV: CONCLUSION	40
APPENDIX A: PROTODECARBOXYLATION - NMR SPECTRA	41
APPENDIX B: ISOMALEIMIDE - NMR SPECTRA	87

LIST OF TABLES

Table 1. Catalyst Screening.....	8
Table 2. Solvent and Base Screening	9
Table 3. Protodecarboxylation Substrate Scope.....	10
Table 4. Optimization of Isomaleimide Reaction Conditions.....	22
Table 5. Isomaleimide Substrate Scope	24
Table 6. Optimization of Protodecarboxylation In Flow	26
Table 7. Flow Synthesis of Select Substrates.....	27

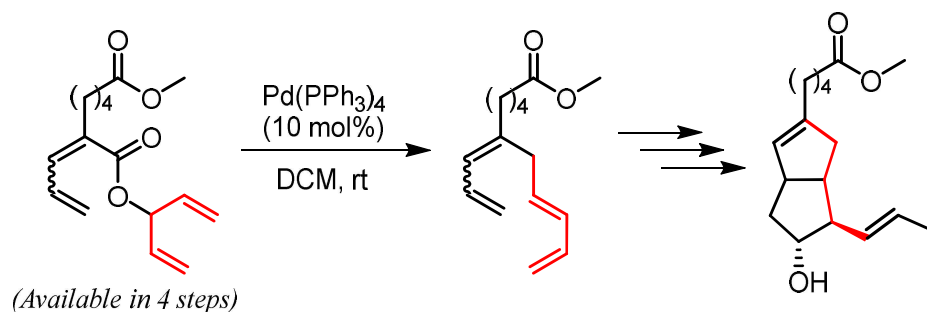
LIST OF SCHEMES

Scheme 1. Decarboxylation in the total synthesis of clinprost.....	1
Scheme 2. Decarboxylative coupling of dienoic acids and pentadienyl alcohol.	1
Scheme 3. Mild palladium-catalyzed protodecarboxylation of dienoic acids.....	2
Scheme 4. Chemoselectivity Experiments for The Protodecarboxylation of Dienoic Acids.....	2
Scheme 5. Early Experiments in the Protodecarboxylation of β -keto Acrylic Acids	2
Scheme 6. Graphical Abstract	5
Scheme 7. A Sampling of Previous Methodologies focused on β -Keto Acrylic Acids.	6
Scheme 8. Initial Experiments Utilizing Ketoenoic Acid Substrates.....	7
Scheme 9. Influence of Triaryl Phosphine Substituents On Dimerization.....	7
Scheme 10 Isomaleimide Graphical Abstract	19
Scheme 11. Dehydration of maleamic Acids to Form Isomaleimides.	19
Scheme 12. One-Flask Synthesis of Isomaleimides From Aniline	28
Scheme 13. General Isomaleimide Synthesis.....	29
Scheme 14. Flow Reaction Setup	30

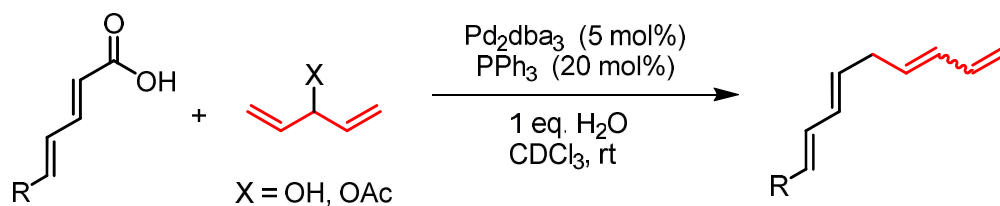
CHAPTER I: INTRODUCTION

Starting with the development of the palladium-catalyzed sequential rearrangement-decarboxylative coupling of bis-allylic dienoates during the synthesis of clinprost ¹ (Scheme 1), an array of palladium-catalyzed reactions were developed. ²⁻⁴ The unique decarboxylative coupling method was further studied and optimized. ² Therein, it was found that the method could perform not only the decarboxylation of bis-allylic dienoates, but it was also useful in the two-component decarboxylative coupling of dienoic acids and pentadienyl alcohols (Scheme 2). This methodology was ultimately applied in the synthesis of isocarbocyclin analogues. ³ During this synthesis, the formation of a new side-product occurred: the protodecarboxylated diene. Further focus on this protodecarboxylation led to the first mild, palladium-catalyzed chemoselective protodecarboxylation of dienoic acids (Scheme 3).⁴

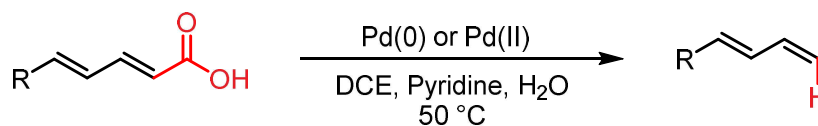
Scheme 1. Decarboxylation in the total synthesis of clinprost.



Scheme 2. Decarboxylative coupling of dienoic acids and pentadienyl alcohol.

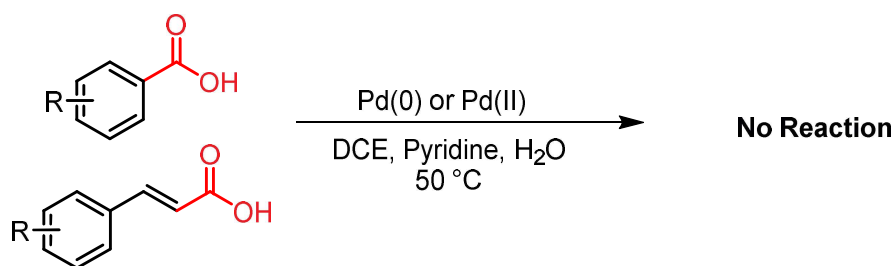


Scheme 3. Mild palladium-catalyzed protodecarboxylation of dienoic acids.



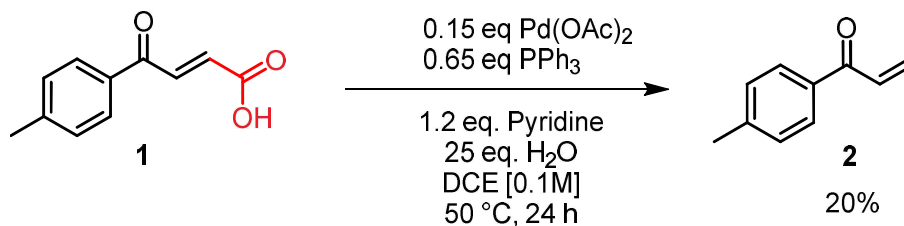
The protodecarboxylation was found to be highly selective for trans dien- and polyenoic acids. Under optimal conditions reported, there was no reactivity of cinnamic or benzoic acids (Scheme 4), showing high chemoselectivity for dienoic acids. One rather unique component of the methodology is its applicability to aryl and aliphatic dienoic acids, with reactivity trends showing favorability for aliphatic substrates.⁴

Scheme 4. Chemoselectivity Experiments for The Protodecarboxylation of Dienoic Acids



This trend in reactivity is in stark contrast to other metal-catalyzed (proto)decarboxylation reactions reported in literature, which often require benzylic or aryl acids.⁵⁻⁶ These reaction conditions were also found to catalyze the protodecarboxylation of one other substrate class: γ -ketoenoic acids (Scheme 5).

Scheme 5. Early Experiments in the Protodecarboxylation of β -keto Acrylic Acids



The achievements mentioned thus far serve as the basis for the work described herein. The protodecarboxylation of ketoenoic acids was the primary focus of my work at the University of North Carolina at Greensboro. My initial efforts focused on reaction optimization. With the assistance of Charles Crawford, Mary-Margaret Crabb, and Ashley Brown, the optimal conditions were screened against a variety of substrates (Chapter 2).

To expand the substrate scope further, maleamic acids were prepared by Dr. Kharul (Fahim) Alam. Upon an early failure with a secondary amide, it was decided that a methane sulfonyl protection of the amide nitrogen might ameliorate the reactivity observed. Upon attempting such a protection, it too was found unsuccessful. However, this attempted reaction led to the uncovering of the isomaleimide synthesis (Chapter 3).

REFERENCES

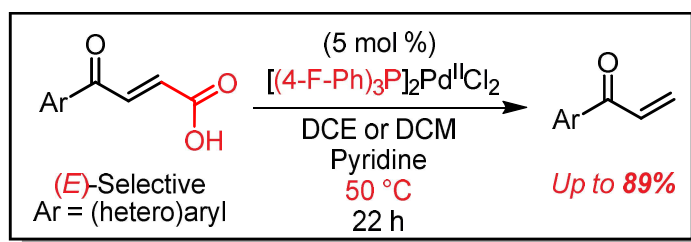
- [¹] Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P. *Organic Letters* **2013**, *15*, 586-589.
- [²] Deiab, G. a. I. A.; Al-Huniti, M. H.; Hyatt, I. F. D.; Nagy, E. E.; Gettys, K. E.; Sayed, S. S.; Joliat, C. M.; Daniel, P. E.; Vummalaneni, R. M.; Morehead, A. T., Jr.; Sargent, A. L.; Croatt, M. P. *Beilstein Journal of Organic Chemistry* **2017**, *13*, 384-392.
- [³] Abu Deiab, G. a. I.; Croatt, M. P. *Bioorganic & Medicinal Chemistry* **2019**, *27*, 338-342.
- [⁴] Al-Huniti, M. H.; Perez, M. A.; Garr, M. K.; Croatt, M. P. *Org Lett* **2018**, *20*, 7375-7379.
- [⁵] Dickstein, J. S.; Curto, J. M.; Gutierrez, O.; Mulrooney, C. A.; Kozlowski, M. C. *The Journal of Organic Chemistry* **2013**, *78*, 4744-4761.
- [⁶] Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I. *Organic Letters* **2009**, *11*, 5710-5713.

CHAPTER II: PROTODECARBOXYLATION OF β -KETO ACRYLIC ACIDS

The Following is adapted from a manuscript currently in preparation for submission to the Journal of Organic Chemistry.

Elvis C. McFee, Charles C. Crawford, Mary-Margaret A. Crabb, Ashley K. Brown, Mohammed H. Al-Huniti, Mitchell P. Croatt*

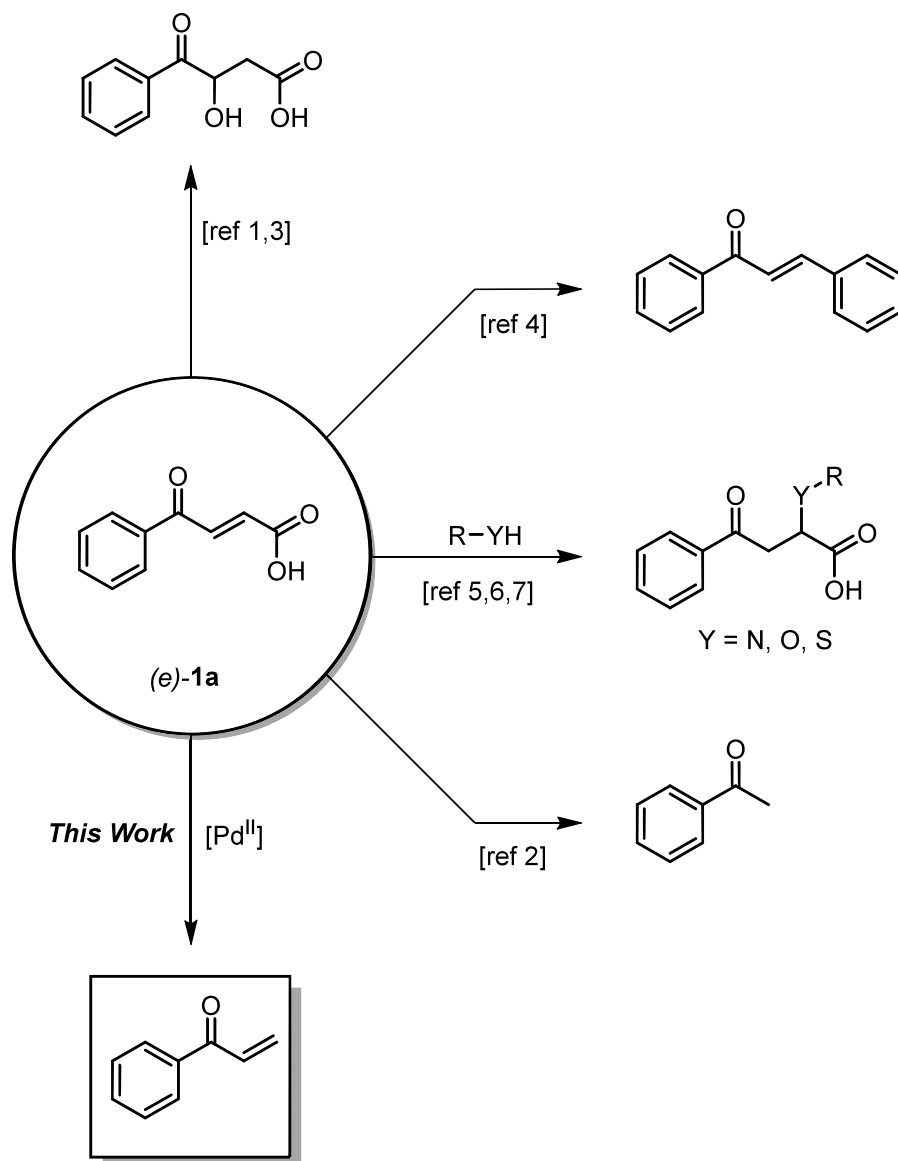
Scheme 6. Graphical Abstract



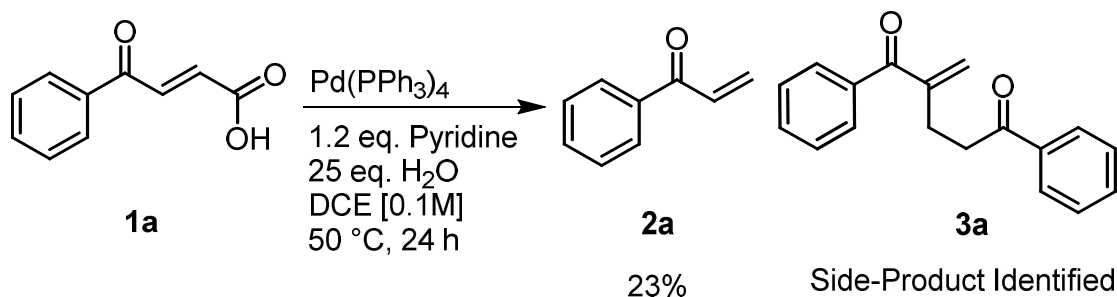
The β -keto acrylic acid moiety was first reported near the turn of the 20th century.¹ Through years of scientific rigor, several transformations to the carbon back-bone have become well established in the literature (**Scheme 7**).²⁻⁷ Herein, the protodecarboxylation methodology previously reported⁸ is further elaborated upon, affording a previously unknown transformation of the β -keto acrylic acid moiety.

Despite the assumed requirement of a conjugated diene system adjacent to the carboxylic acid, this hetero-diene successfully underwent protodecarboxylation. Early studies revealed that the previous methodology was not perfectly amendable to this class of substrates, as dimerization of the product dominated (**Scheme 8**). Therefore, the re-optimization of the reaction was initiated towards achieving the desired transformation.

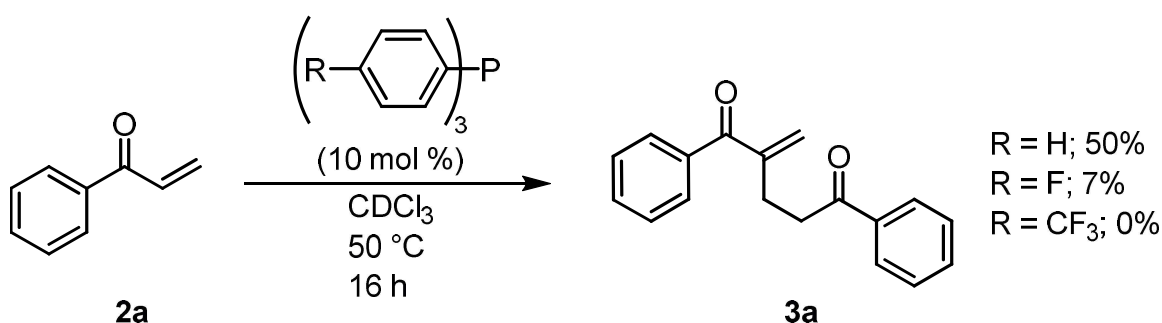
Scheme 7. A Sampling of Previous Methodologies focused on β -Keto Acrylic Acids.



Scheme 8. Initial Experiments Utilizing Ketoenoic Acid Substrates.



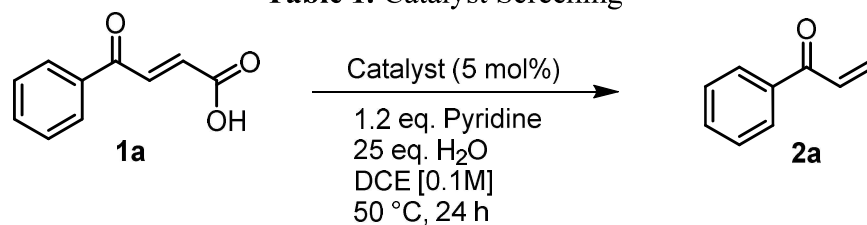
Scheme 9. Influence of Triaryl Phosphine Substituents On Dimerization



With this reaction hypothesized to occur through a Rauhut-Currier mechanism, a selection of phosphine ligands was screened to assess their propensity to transform product **2a** into dimer **3a** (Scheme 9).

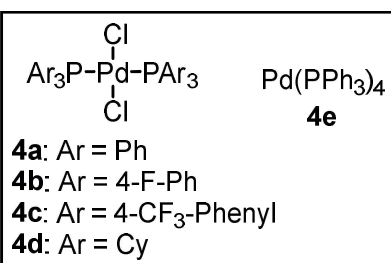
To curtail this undesirable dimerization observed in the protodecarboxylation, the catalysts were prepared using the aforementioned phosphine ligands (Table 1).

Bis(triphenylphosphine)palladium^{II} dichloride (**4a**), showed notable improvement in product selectivity with decreased catalyst loading (Table 1, entries **1** vs **10**). The analogous tris(4-fluorophenyl)phosphine catalyst **4b** was observed to exist in an apparent goldilocks zone of reactivity – with the electron-deficient phosphine serving as an effective ligand to the palladium without the nucleophilicity required for any observable dimerization to occur. Catalyst **4b** was also observed to facilitate the transformation without the addition of water. This is an important feat, given the general scalability issues associated with biphasic reaction systems.

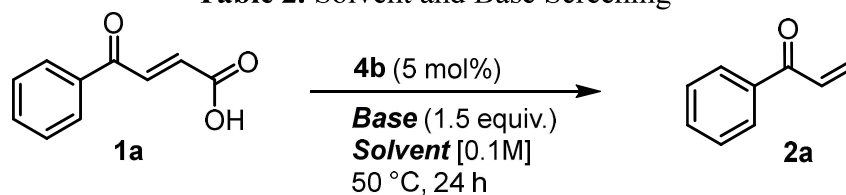
Table 1. Catalyst Screening

Entry	Catalyst	% Yield 2a
1	4a	61 ^a
2	4b	92
3 ^b	4b	95
4	4c	37
5	4d	0
6	4e	23 ^a

Yields determined via quantitative ¹H NMR. Unless otherwise noted, no dimer **3a** was observed. [a] Reaction presumed limited by the formation of dimer **3a**. [b] Reaction performed without the addition of water.



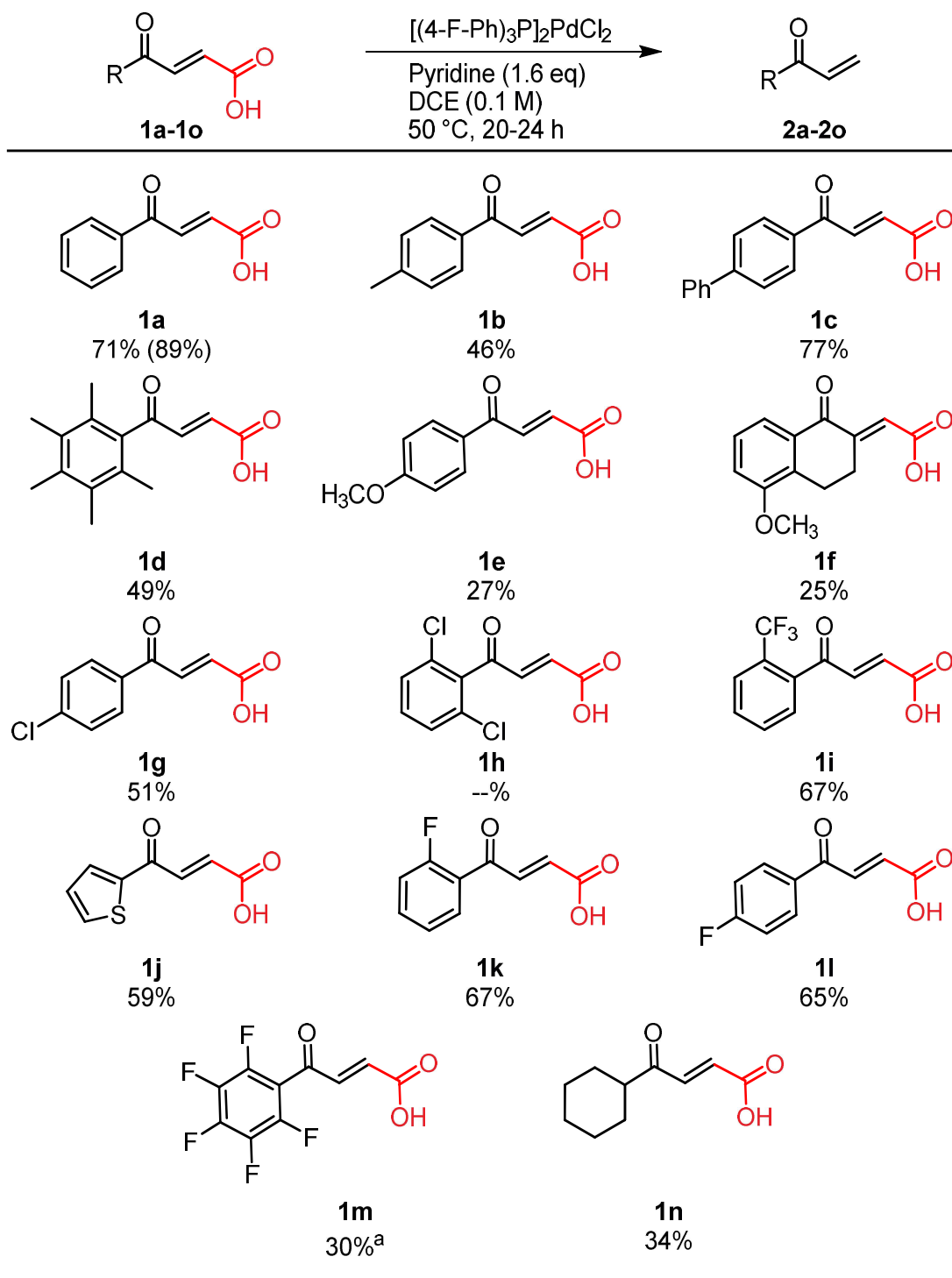
Following the breakthrough results accomplished with catalyst **4b**, a selection of alternative solvents was screened. While MeCN and 2,2,2-trifluoroethanol showed subpar results (**Table 2**, **entries 4-5**), dimethyl carbonate and EtOAc showed comparable reactivity to DCE (**Table 2**, **entries 1-3**). Upon screening organic bases, a general, inverse correlation was observed between pK_a and the product yields. This trend may be attributed to protodepalladation, in which a stronger base would create a bottleneck in catalyst recycling.

Table 2. Solvent and Base Screening

Entry	Solvent	Base	% Yield
1	DCE	Pyridine	95
2	Dimethyl Carbonate	Pyridine	89 ^a
3	Ethyl Acetate	Pyridine	92
4	2,2,2-trifluoroethanol	Pyridine	0
5	MeCN	Pyridine	18
6 ^b	DCE	2,6-lutidine	87
7 ^b	DCE	DMAP	13
8 ^b	DCE	Et ₃ N	3

Unless otherwise stated, all yields are determined by quantitative NMR with Dimethyl terephthalate as internal standard. a) yield represents isolated product b) NMR yields determined using DCE as internal standard.

Upon completion of the optimization, the applicability of the reaction was assessed for an array of beta-aryl acrylic acids (**Table 4**). In general, substrates bearing only aryl ring(s) (**1a**, **1c**) performed the best (71% & 77%). Upon substitution with electron donating groups (**1e**, **1f**), a notable yield drop was observed. The analogous heteroaromatic substrate **1j**, performed comparably well to substrates bearing electron withdrawing groups (**1i**, **1k**, **1l**). To our surprise, the pentafluoro-phenyl substrate **1m** did not yield the anticipated enone **2m**. In this case the only product observed was the corresponding dimer **3m**, likely resulting from rapid dimerization due to the heightened electrophilicity of the beta-enone position of **2m**.

Table 3. Protodecarboxylation Substrate Scope

Reported yields are of isolated products obtained under reaction conditions shown, unless otherwise indicated. Parentetical yields represent product isolated from reaction utilizing dimethyl carbonate as solvent. a) Product exclusively yielded the corresponding dimer **3m**.

The herein reported palladium catalyzed protodecarboxylation represents the first method developed for the selective conversion of readily accessible β -keto acrylic acids to their corresponding terminal enone products. This reaction is especially unique in comparison to other protodecarboxylation methodologies due to its mild reaction conditions and applicability to non-aromatic systems.

Experimental

GENERAL INFORMATION

NMR spectra were recorded on a 400/500 MHz (^1H) or 100/125 (^{13}C) JEOL spectrometer. Chemical shifts (δ) and coupling constants (J) are given in parts per million (ppm) and in hertz (Hz), respectively. Catalyst prepared using sodium tetrachloropalladate (Engelhard). Microwave reactions performed in a CEM Discover benchtop reactor. Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification.

GENERAL CONDITIONS FOR THE SYNTHESIS OF SUBSTRATES (A)

To a clean, dry 6 mL microwave vial fitted with a stir bar, the corresponding aryl methyl ketone (3.0 mmol) and glyoxylic acid (3.6 mmol, 1.2 eq.) are dissolved in glacial acetic acid (6.0 mL). The vial is capped, and the solution is extensively purged with $\text{N}_{2(\text{g})}$ via a needle pierced through the vial septum (5-10 min.). The vial is then heated to 150 °C for 3 hours, followed by additional heating to 175 °C to 1 hour. Upon completion, the reaction is cooled to room temperature and the product isolated by crystallization or flash column chromatography. Crystallizations performed by first azeotropically removal of acetic acid with toluene via rotary evaporation, then dissolving the crude solid in minimal hot toluene, and slowly cooling to room temperature in a crystalizing dish. Column chromatography performed using SiliaFlash® P60 silica gel and gradient elution with mixtures of hexane-EtOAc with 0.1%-1.0% AcOH added.

GENERAL PROTODECARBOXYLATION PROCEDURE

To a clean, dry 6 mL microwave vial fitted with a stir bar, **1** (0.1 mmol), **4c** (0.005 mmol, 4.1 mg), and DCE (1.0 mL), and pyridine (0.12 mmol, 11 μ L) are sequentially added. The vial is purged with N_{2(g)}, capped, and stirred in an oil bath (50 °C) for 22 hours. Upon completion, the reaction is cooled to room temperature, and directly loaded onto a flash column packed in 2% Et₂O/Pentane and eluted with a stepwise gradient (2% \rightarrow 30%). Collected fractions are carefully reduced under vacuum, yielding the desired product **2**. Use of prolonged rotary-evaporation or any use high-vacuum was found to result in substantial loss of products due to volatility. product purity is indicated by ¹H NMR (See Appendix A)

SPECTROSCOPIC DATA

1c ¹H NMR (400 MHz, CD₂Cl₂) δ 8.07 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 15.5 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.65 (dt, J = 8.4, 2.2 Hz, 2H), 7.47 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 6.87 (d, J = 15.5 Hz, 1H). ¹³C NMR (101 MHz, DMSO-D₆) δ 189.44, 166.89, 145.84, 139.19, 136.73, 135.50, 133.39, 130.12, 129.69, 129.16, 127.74, 127.61.

1d ¹H NMR (400 MHz, CD₃OD) δ 6.93 (d, J = 16.0 Hz, 1H), 6.23 (d, J = 16.0 Hz, 1H), 2.24 (s, 3H), 2.18 (s, 6H), 2.01 (s, 6H). ¹³C NMR (126 MHz, CD₃OD) δ 205.52, 170.93, 141.66, 140.00, 138.30, 137.05, 134.12, 129.82, 17.63, 16.82, 16.02.

1f ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.87 (t, J = 1.8 Hz, 1H), 3.42 (td, J = 6.4, 1.6 Hz, 2H), 3.01 (t, J = 6.4 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 187.12, 171.45, 156.55, 152.30, 133.38, 127.65, 122.08, 120.03, 115.03, 55.86, 26.89, 21.66.

1h ¹H NMR (400 MHz, MeCN-D₃) δ 7.51 – 7.39 (m, 3H), 7.15 (d, J = 16.1 Hz, 1H), 6.46 (d, J = 16.1 Hz, 1H). ¹³C NMR (101 MHz, MeCN-D₃) δ 193.49, 166.18, 139.79, 137.37, 136.33, 132.99, 131.94, 129.55, 118.32.

1i ¹H NMR (400 MHz, DMSO-D₆) δ 7.90 (d, J = 7.6 Hz, 1H), 7.85 – 7.77 (m, 2H), 7.74 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 16.0 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H). ¹³C NMR (126 MHz, CD₃OD) δ 195.55, 167.84, 140.57, 140.57, 138.66, 138.65, 136.86, 133.39, 133.38, 132.15, 129.60,

129.59, 129.58, 129.57, 129.16, 128.91, 128.65, 128.39, 128.29, 128.06, 128.02, 127.98, 127.94, 126.13, 123.95, 121.78. ^{19}F NMR (376 MHz, CD_3OD) δ -59.22.

1j ^1H NMR (400 MHz, DMSO-D_6) δ 8.24 (d, J = 3.7 Hz, 1H), 8.16 (d, J = 4.7 Hz, 1H), 7.84 (d, J = 15.4 Hz, 1H), 7.36 – 7.28 (m, 1H), 6.72 (d, J = 15.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-D_6) δ 181.26, 166.29, 143.84, 137.31, 135.61, 135.35, 132.59, 129.39, 39.52.

1k ^1H NMR (400 MHz, ACETONE-D_6) δ 11.50 (s, 1H), 7.85 (td, J = 7.6, 1.8 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.69 (d, J = 3.2 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.34 (dd, J = 11.2, 8.5 Hz, 1H), 6.73 (dd, J = 15.6, 0.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-D_6) δ 188.11, 166.24, 162.19, 159.67, 138.85, 135.79, 135.70, 132.83, 130.86, 125.16, 117.04, 116.82. ^{19}F NMR (376 MHz, CD_3OD) δ -112.39.

1l ^1H NMR (400 MHz, ACETONE-D_6) δ 11.47 (s, 1H), 8.22 – 8.16 (m, 1H), 7.95 (d, J = 15.6 Hz, 1H), 7.40 – 7.31 (m, 1H), 6.78 (d, J = 15.6 Hz, 1H). ^{13}C NMR (126 MHz, METHANOL-D_3) δ 189.62, 168.64, 168.36, 166.61, 137.38, 134.61, 134.59, 133.99, 132.95, 132.87, 117.14, 116.96. ^{19}F NMR (471 MHz, CD_3OD) δ -106.21.

1m ^1H NMR (400 MHz, ACETONITRILE-D_3) δ 9.76 (s, 1H), 7.29 (dt, J = 15.9, 1.5 Hz, 1H), 6.70 (d, J = 15.9 Hz, 1H). ^{13}C NMR (101 MHz, METHANOL-D_3) δ 192.03, 147.30, 141.01, 137.12, 133.53, 130.67, 130.49, 130.09, 129.42, 128.32, 128.23.

1n ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 5.5 Hz, 1H), 6.11 (d, J = 5.5 Hz, 1H), 2.56 – 2.48 (m, 2H), 2.39 – 2.32 (m, 2H), 1.72 – 1.58 (m, 7H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 202.24, 170.59, 140.30, 129.69, 50.01, 28.16, 25.83, 25.60.

2a ^1H NMR (400 MHz, CDCl_3) δ 7.95 – 7.92 (m, 1H), 7.56 (dt, J = 8.5, 1.2 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.15 (dd, J = 17.2, 10.6 Hz, 1H), 6.43 (dd, J = 17.1, 1.6 Hz, 1H), 5.93 (dd, J = 10.6, 1.6 Hz, 1H). Spectroscopic data agrees with the literature. ¹⁰

2b ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, J = 8.2 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.17 (dd, J = 17.1, 10.6 Hz, 1H), 6.43 (dd, J = 17.2, 1.7 Hz, 1H), 5.90 (dd, J = 10.5, 1.7 Hz, 1H), 2.42 (s, 2H). Spectroscopic data agrees with the literature. ¹¹

2c ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.41 (t, J = 7.3 Hz, 1H), 7.22 (dd, J = 17.1, 10.6 Hz, 1H), 6.48 (dd, J = 17.1, 1.6 Hz, 1H), 5.96 (dd, J = 10.5, 1.6 Hz, 1H). Spectroscopic data agrees with the literature.¹²

2d ^1H NMR (400 MHz, CDCl_3) δ 6.57 (dd, J = 17.6, 10.4 Hz, 1H), 6.07 (dd, J = 10.4, 1.0 Hz, 1H), 5.88 (dd, J = 17.6, 1.0 Hz, 1H), 2.24 (s, 3H), 2.19 (s, 6H), 2.06 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 203.63, 138.85, 137.14, 135.63, 132.91, 132.68, 129.01, 17.52, 16.82, 16.04.

2e ^1H NMR (500 MHz, CDCl_3) δ 7.99 – 7.95 (m, 1H), 7.18 (dd, J = 17.1, 10.5 Hz, 1H), 6.98 – 6.94 (m, 1H), 6.43 (dd, J = 17.1, 1.8 Hz, 1H), 5.88 (dd, J = 10.5, 1.8 Hz, 1H), 3.88 (s, 3H). Spectroscopic data agrees with the literature.¹²

2f ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 7.9 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 8.6 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.18 (d, J = 1.0 Hz, 1H), 5.43 (d, J = 1.3 Hz, 1H), 3.87 (s, 3H), 2.96 (t, J = 6.4 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 187.96, 156.54, 143.46, 134.16, 127.26, 121.38, 119.78, 114.42, 55.79, 31.02, 22.55. Spectroscopic data agrees with the literature.¹²

2g ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.11 (dd, J = 17.1, 10.6 Hz, 1H), 6.43 (dd, J = 17.1, 1.5 Hz, 1H), 5.94 (dd, J = 10.6, 1.4 Hz, 1H). Spectroscopic data agrees with the literature.¹²

2h ^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.27 (m, 3H), 6.59 (dd, J = 17.7, 10.5 Hz, 1H), 6.20 (d, J = 10.5 Hz, 1H), 5.98 (d, J = 17.6 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 193.55, 137.21, 136.44, 133.73, 131.86, 130.86, 128.21.

2i ^1H NMR (400 MHz, CDCl_3) δ 7.76 – 7.70 (m, 1H), 7.66 – 7.54 (m, 2H), 7.42 – 7.36 (m, 1H), 6.68 (dd, J = 17.7, 10.6 Hz, 1H), 6.15 (d, J = 10.6 Hz, 1H), 5.96 (d, J = 17.6 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 195.82, 137.93, 137.01, 133.69, 131.63, 130.13, 128.27, 128.19, 127.95, 127.73, 127.63, 126.90, 126.86, 126.81, 126.76, 125.01, 122.29, 119.56.

2j ^1H NMR (400 MHz, CDCl_3) δ 7.79 (dd, J = 3.8, 0.9 Hz, 1H), 7.69 (dd, J = 5.0, 0.8 Hz, 1H), 7.17 (dd, J = 4.8, 3.9 Hz, 1H), 7.09 (dd, J = 17.0, 10.4 Hz, 1H), 6.51 (dd, J = 17.0, 1.5 Hz, 1H),

5.89 (dd, $J = 10.4, 1.5$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 182.59, 144.73, 134.50, 132.58, 131.95, 129.68, 128.41, 77.16.

2k ^1H NMR (400 MHz, CDCl_3) δ 7.79 (td, $J = 7.5, 1.8$ Hz, 1H), 7.56 (tdd, $J = 7.1, 5.1, 1.8$ Hz, 1H), 7.29 (d, $J = 7.5$ Hz, 1H), 7.18 (dd, $J = 10.6, 8.6$ Hz, 1H), 7.06 (ddd, $J = 17.1, 10.4, 3.1$ Hz, 1H), 6.43 (dt, $J = 16.9, 1.5$ Hz, 1H), 5.96 (dd, $J = 10.3, 1.3$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 189.78 (s), 161.37 (d, $J = 253.9$ Hz), 135.58 (d, $J = 6.1$ Hz), 134.25 (d, $J = 8.9$ Hz), 130.73 (d, $J = 67.6$ Hz), 126.27 (s), 124.57 (d, $J = 3.5$ Hz), 116.63 (d, $J = 23.0$ Hz). ^{19}F NMR (376 MHz, CDCl_3) δ -110.53.

2l ^1H NMR (400 MHz, CDCl_3) δ 8.04 – 7.95 (m, 1H), 7.19 – 7.09 (m, 2H), 6.44 (d, $J = 17.2$ Hz, 1H), 5.94 (d, $J = 10.5$ Hz, 1H). Spectroscopic data agrees with the literature.^{11,12}

2n ^1H NMR (400 MHz, CDCl_3) δ 6.43 (dd, $J = 17.5, 10.4$ Hz, 1H), 6.25 (d, $J = 16.3$ Hz, 1H), 5.75 (d, $J = 10.5$ Hz, 1H), 2.67 – 2.57 (m, 1H), 1.89 – 1.64 (m, 6H), 1.44 – 1.27 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 203.70, 135.02, 127.91, 48.24, 28.60, 25.94, 25.76. Spectroscopic data agrees with the literature.¹²

3a ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 7.7$ Hz, 1H), 7.55 (q, $J = 7.6$ Hz, 1H), 7.45 (dd, $J = 17.8, 7.7$ Hz, 2H), 5.98 (s, 1H), 5.69 (s, 1H), 3.25 (t, $J = 7.4$ Hz, 1H), 2.92 (t, $J = 7.3$ Hz, 1H).

3m ^1H NMR (500 MHz, CDCl_3) δ 6.31 (s, 1H), 5.88 (s, 1H), 3.15 (t, $J = 7.1$ Hz, 2H), 2.90 (t, $J = 7.0$ Hz, 2H).

REFERENCES

1. Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P., Sequential Pd(0)-, Rh(I)-, and Ru(II)-Catalyzed Reactions in a Nine-Step Synthesis of Clinprost. *Org. Lett.* **2013**, *15* (3), 586-589.
2. Deiab, G. a. I. A.; Al-Huniti, M. H.; Hyatt, I. F. D.; Nagy, E. E.; Gettys, K. E.; Sayed, S. S.; Joliat, C. M.; Daniel, P. E.; Vummalaneni, R. M.; Morehead, A. T., Jr.; Sargent, A. L.; Croatt, M. P., Decarboxylative and dehydrative coupling of dienolic acids and pentadienyl alcohols to form 1,3,6,8-tetraenes. *Beilstein Journal of Organic Chemistry* **2017**, *13*, 384-392.
3. Abu Deiab, G. a. I.; Croatt, M. P., Synthetic approaches to isocarbacyclin and analogues as potential neuroprotective agents against ischemic stroke. *Biorg. Med. Chem.* **2019**, *27* (2), 338-342.
4. Al-Huniti, M. H.; Perez, M. A.; Garr, M. K.; Croatt, M. P., Palladium-Catalyzed Chemoselective Protodecarboxylation of Polyenoic Acids. *Org. Lett.* **2018**, *20* (23), 7375-7379.
5. Dickstein, J. S.; Curto, J. M.; Gutierrez, O.; Mulrooney, C. A.; Kozlowski, M. C., Mild Aromatic Palladium-Catalyzed Protodecarboxylation: Kinetic Assessment of the Decarboxylative Palladation and the Protodepalladation Steps. *The Journal of Organic Chemistry* **2013**, *78* (10), 4744-4761.
6. Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I., Silver-Catalyzed Protodecarboxylation of Heteroaromatic Carboxylic Acids. *Org. Lett.* **2009**, *11* (24), 5710-5713.
7. Gras, J.-L., A facile entry to vinyl ketones. *Tetrahedron Letters* **1978**, *19* (32), 2955-2958.
8. Bugarin, A.; Jones, K. D.; Connell, B. T., Efficient, direct α -methylenation of carbonyls mediated by diisopropylammonium trifluoroacetate. *Chemical Communications* **2010**, *46* (10), 1715-1717.
9. Verma, F.; Shukla, P.; Bhardiya, S. R.; Singh, M.; Rai, A.; Rai, V. K., Photocatalytic C(sp³)-H Activation towards α -methylenation of Ketones using MeOH as 1 C Source Steering Reagent. **2019**, *361* (6), 1247-1252.
10. Urawa, Y.; Nishiura, K.; Souda, S.; Ogura, K., A Convenient Method for Preparing Aromatic α,β -Unsaturated Ketones from α,β -Unsaturated Acyl Chlorides and Arylboronic Acids via Suzuki-Miyaura Type Coupling Reaction. *Synthesis* **2003**, *2003* (18), 2882-2885.
11. An, X.-L.; Chen, J.-R.; Li, C.-F.; Zhang, F.-G.; Zou, Y.-Q.; Guo, Y.-C.; Xiao, W.-J., Highly Efficient Route to Functionalized Tetrahydrocarbazoles Using a Tandem Cross-Metathesis/Intramolecular-Hydroarylation Sequence. *Chemistry – An Asian Journal* **2010**, *5* (10), 2258-2265.
12. Pandey, G.; Vaitla, J., Desulfonylative Methenylation of β -Keto Sulfones. *Organic Letters* **2015**, *17* (19), 4890-4893.

CHAPTER III: SYNTHESIS OF ISOMALEIMIDES BY DEHYDRATION OF MALEAMIC ACIDS USING METHANESULFONYL CHLORIDE

PREFACE

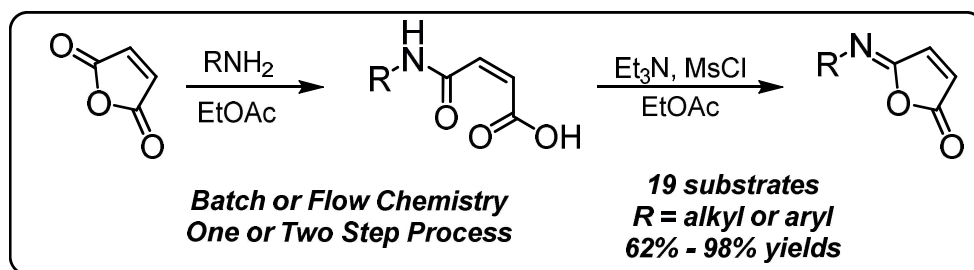
The previously discussed work was initiated around October 2019, shortly after joining the Croatt lab group. Around December 2019 Dr. Kharul Alam joined the group as a post-doctoral researcher. As a portion of his early research efforts, Dr. Alam synthesized a unique substrate to trial under the protodecarboxylation conditions – a maleamic acid. This early effort showed no reactivity, which was hypothesized to occur due to coordination of the amide nitrogen to the palladium catalyst. To circumvent this, Dr. Alam attempted to protect the nitrogen using methane sulfonyl chloride. While the reaction was unsuccessful in facilitating the desired protection, an unexpected product was formed – an isomaleimide. This discovery led to the title manuscript preparation.

The reaction was observed to occur rapidly, which encouraged us to ask *How Fast* the reaction really is. To address this question, I set out to study the reaction in a continuous flow reaction system. In addition to assisting in the batch syntheses substrate scope, my primary contributions to the project were in re-programing and utilizing the 3D Printed flow system developed previously in the Croatt Group.

The Following is adapted from the most up-to-date iteration of the Journal of Organic Chemistry manuscript in preparation.

Khyarul Alam, Elvis C. McFee and Mitchell P. Croatt*

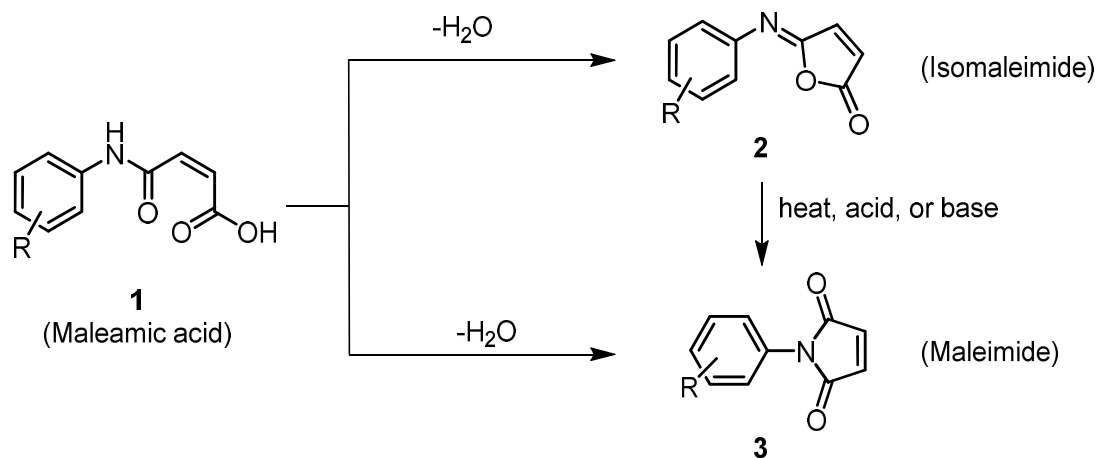
Scheme 10 Isomaleimide Graphical Abstract



ABSTRACT: The dehydration of maleamic acids using methanesulfonyl chloride as a dehydrating agent to generate isomaleimides selectively and rapidly (<15 min.) is reported. A variety of maleamic acid derivatives produce the corresponding isomaleimides in good to excellent yields. Adaptation of this protocol under flow synthesis allows for similar efficiency and decreased reaction times (13 sec. residence time). It was also possible to convert maleic anhydride to the desired isomaleimide in a two-step, one-flask operation.

Dehydration of maleamic acids results in the formation of maleimides and isomaleimides, depending on the conditions for ring closure (Scheme 11).³ Isomaleimides are typically the kinetically favored product while maleimides are preferred thermodynamically. Isomaleimides are known to thermally isomerize to maleimides, which is greatly accelerated by the presence of an acid or base catalyst.⁴ Despite the growing body of work utilizing maleimides in organic synthesis,⁵ the formation or use of isomaleimides has received little attention.⁶ Since the first isomaleimide synthesis reported in 1955,^{2a} there have been few general and efficient methods reported to form this interesting molecular scaffold.⁷ The synthesis of isomaleimides by dehydration of maleamic acid suffers from the lack of appropriate dehydrating agents, use of toxic reagents, longer reaction times, decomposition of maleamic acids, and poor selectivity in the ring closure, giving mixtures of maleimides and isomaleimides.^{2,3,4,7} Therefore, development of a rapid, efficient, and green synthesis of isomaleimides remains a challenge.

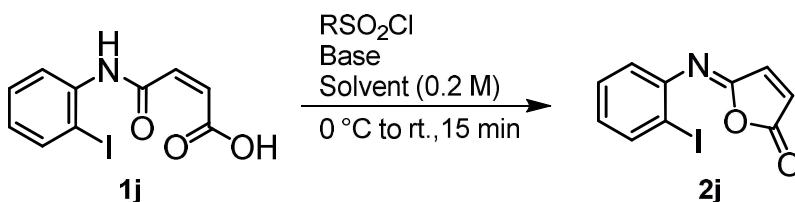
Scheme 11. Dehydration of maleamic Acids to Form Isomaleimides.



During the Croatt Group's research into carboxylate derivatizations,⁸ it was found the maleamic acid **1j** underwent rapid dehydration rendering isomaleimide **2j** in 85% yield when treated with methanesulfonyl chloride (MsCl) in pyridine (Table 4, entry 1). Since there are increasing interests in isomaleimide chemistry with recent useful applications in polyisoimides,⁹ gelatin hardeners,¹⁰ herbicide antidotes,^{3a} *in vivo* photodynamic therapy,¹¹ and enzyme inhibition,^{6b} efforts were made to establish a general and efficient method of isomaleimide preparation. Herein, is reported a rapid, green, and facile synthesis of isomaleimides using methanesulfonyl chloride as the dehydrating agent.

The optimization of the reaction conditions used maleamic acid **1j** as the model substrate (Table 4). The reaction of maleamic acid **1j** with methanesulfonyl chloride in pyridine at room temperature resulted in full conversion after 3 h (entry 1). There was no reaction in the absence of a base, leaving starting material intact (entry 2). The use of 3.0 equiv. of MsCl and 3.0 equiv. of pyridine as a base in DCM resulted in rapid cyclization within less than 15 minutes, yielding product **2j** in 87% yield (entry 3). Triethylamine and DIPEA (*N,N*-diisopropylethylamine) showed similar reactivity (89% and 86%, respectively) while DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) resulted in a lower yield (40%) and the formation of an unidentified intermediate by ¹H NMR (entries 4-6). The use of an inorganic base, such as K₂CO₃, was found to be unsuitable for this dehydration process, yielding product in only 10% (entry 7). For reasons of efficiency and ease of removal, Et₃N was chosen as the optimal base for further screening. It was determined that 3.0 equiv. of MsCl and 3.0 equiv. of Et₃N was the most

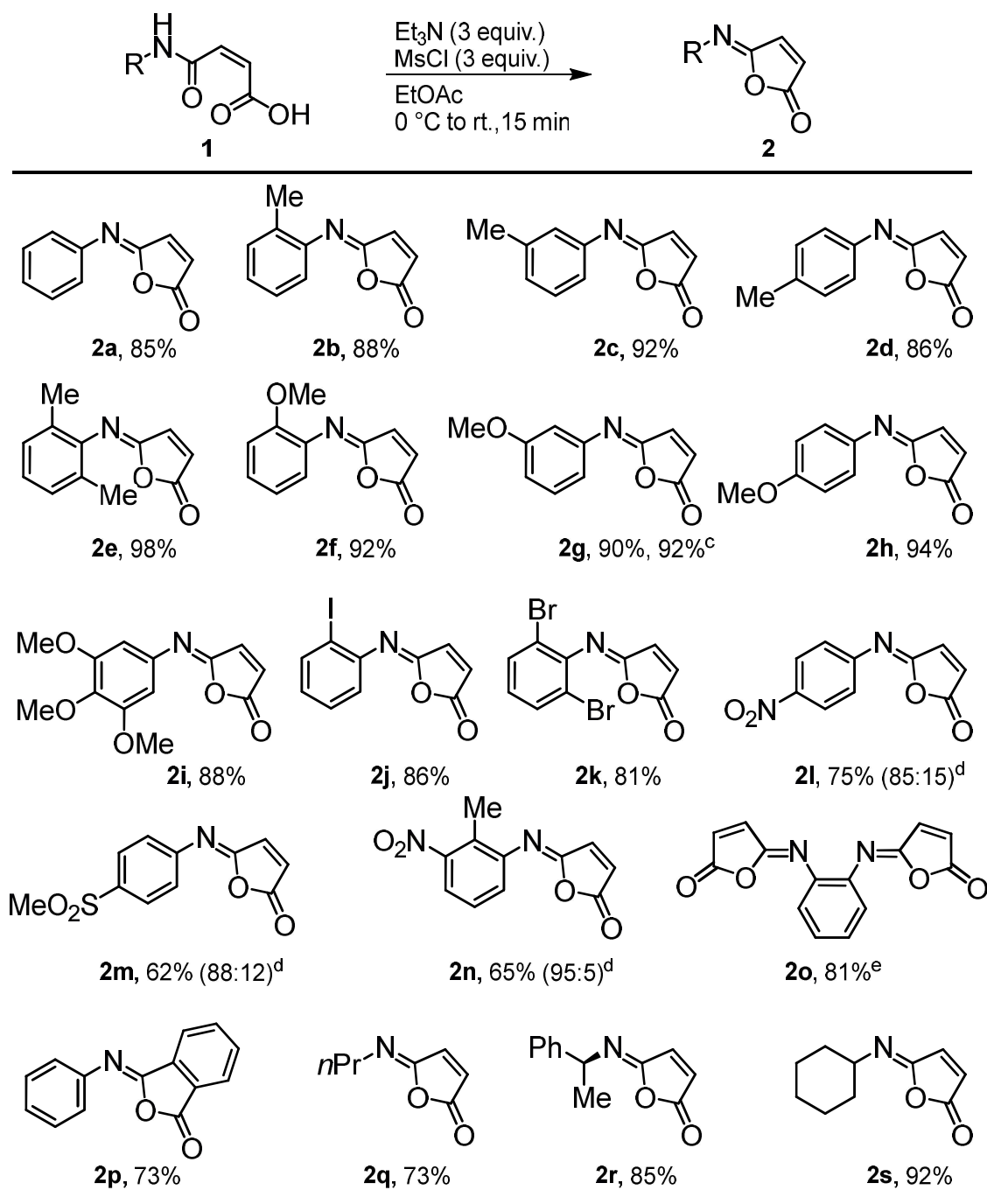
effective ratio among those examined (entry 4 vs. entries 8-10). Screening of solvents revealed that dehydrative cyclization proceeded more efficiently in ethyl acetate (EtOAc), yielding product in an 88% yield, compared to other solvents such as tetrahydrofuran (THF), dioxane, toluene, and acetonitrile (MeCN; entries 11-15). Since EtOAc is commonly accepted as a green solvent ¹² it was selected over DCM for this transformation (entry 4 vs. entry 11). Another sulfonyl chloride derivative, *p*-toluenesulfonyl chloride (TsCl), was tested which resulted in a slight decrease in yield to 68% (entry 16).

Table 4. Optimization of Isomaleimide Reaction Conditions

Entry	RSO ₂ Cl (equiv)	Base (equiv)	Solvent	1j/2j (%) ^b
1 ^c	MsCl (1.5)	-	Pyridine	-/85
2 ^c	MsCl (1.5)	-	DCM	nr.
3	MsCl (3.0)	Pyridine (3.0)	DCM	-/87
4	MsCl (3.0)	Et ₃ N (3.0)	DCM	-/89
5	MsCl (3.0)	DBU (3.0)	DCM	-/40
6	MsCl (3.0)	DIPEA (3.0)	DCM	-/86
7 ^d	MsCl (3.0)	K ₂ CO ₃ (3.0)	DCM	n.d./10
8	MsCl (1.0)	Et ₃ N (2.5)	DCM	39/60
9	MsCl (2.0)	Et ₃ N (2.5)	DCM	31/66
10	MsCl (3.0)	Et ₃ N (2.0)	DCM	10/75
11	MsCl (3.0)	Et ₃ N (3.0)	EtOAc	-/88
12	MsCl (3.0)	Et ₃ N (3.0)	THF	-/80
13	MsCl (3.0)	Et ₃ N (3.0)	Dioxane	28/56
14	MsCl (3.0)	Et ₃ N (3.0)	Toluene	-/85
15	MsCl (3.0)	Et ₃ N (3.0)	MeCN	-/81
16	TsCl (3.0)	Et ₃ N (3.0)	EtOAc	-/68

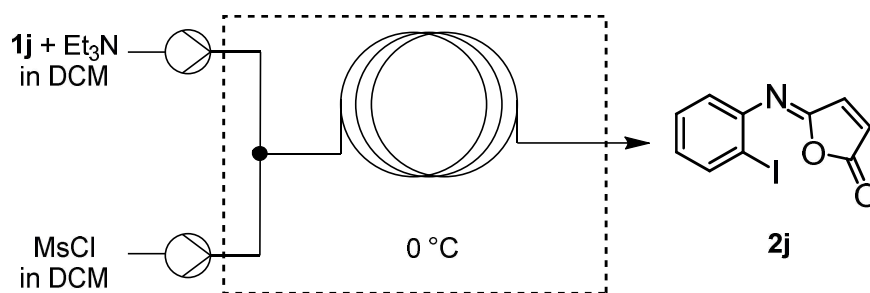
[a] Reaction conditions (unless otherwise noted): reactions were carried out with substrate **1j** (0.1 mmol) in solvent (0.2 M) at room temperature for 15 minutes; [b] ¹H NMR yield using 1,3,5-trimethoxybenzene as the internal standard, **1j** observed as the carboxylate; [c] 3 h reaction; [d] starting material remained but the amount was not determined due to incomplete deprotonation.

With the optimized conditions in hand, the generality of the reaction conditions were investigated by testing a variety of *N*-alkyl/aryl substituted maleamic acid derivatives (Table 5). Rearrangement of isomaleimides to maleimides is a competing reaction and isomaleimides are prone to hydrolysis during work-up, however, the use of dilute NaOH (~ 5% w/v aqueous solution) for quenching and immediate work-up minimized this problem and increased selectivity for isomaleimides while maintaining good to excellent yields.^{2c} It is noteworthy that, although in most cases the *syn*-isoamide (or *Z*-isoamide) products were predominantly formed, an isomeric mixture was also observed in ¹H and ¹³C NMR for some isomaleimide derivatives. Under the optimized conditions, *N*-phenyl maleamic acid gave isomaleimide **2a** in 85% yield. Maleamic acid derivatives containing electron donating groups, such as -Me and -OMe groups on *-ortho*, *-meta* and *-para* positions of the *N*-phenyl substituents, gave products **2b-i** in excellent yields (86-98%). The reactions containing halogen substituents also proceeded smoothly, affording products **2j-k** in 81-87% yields. An electron withdrawing group, such as -NO₂ or -SO₂Me, on the *N*-phenyl ring, however, produced inseparable mixtures of maleimides **3l-n** and isomaleimides **2l-n**. This is assumed to be a result of lowering the activation barrier for the hydrolysis/ring closure to generate the thermodynamic maleimide products. A bis-maleamic acid (**1o**) was also tolerated under the current protocol giving bisisomaleimide product **2o** in 81% yield. The dehydration reactions of phthalanilic acid **1p** gave corresponding isophthalimide **2p** in 73% yield. Interestingly, this protocol can also be applied for the preparation of *N*-alkylisomaleimides as *N*-alkylmaleamic acids gave corresponding isomaleimides **2q-s** in 73-92% yields. As exemplified by maleamic acid **1g**, isomaleimide was readily synthesized on a 1 mmol scale, giving product **2g** with a 92% yield.

Table 5. Isomaleimide Substrate Scope

[a] Reaction conditions (unless otherwise noted): reactions were carried out with substrate **1** (0.2 mmol), MsCl (0.6 mmol), and Et_3N (0.6 mmol) in EtOAc (0.2 M) at $0\text{ }^\circ\text{C}$ to rt.; [b] isolated yields; [c] 1 mmol scale, 188 mg of **2g** isolated; [d] combined yield and ratio (shown in parenthesis) of an inseparable mixture of isomaleimide and maleimide; [e] 6.0 equiv of MsCl and 6.0 equiv of Et_3N were used.

We next examined the dehydration process using a continuous flow system by first reexamining the optimal reaction conditions (Table 6). Due to clogging of the microfluidic tube following precipitation of triethylammonium chloride when ethyl acetate was utilized, dichloromethane was used for all flow reactions performed. By varying the ratios of reagents with a constant flow rate of 3 mL/min (1.5 mL/min for each syringe pump) and 13 seconds of residence time, it was determined that the use of 3 equiv. of Et₃N and 3 equiv. of MsCl was optimal for this transformation (entry 6 vs. entries 1-5), which is consistent with the batch reaction optimization. Increased flow rates resulted in an apparent plateau of reactivity, likely because of decreased residence times coupled with increased mixing efficiency (entry 7 vs. entries 8-10).¹³ An improved yield was observed when the residence time was increased (entry 8 vs. entry 11). Based on the yields and operational ease, it was decided that use of 3 mL/min overall flow rate (13 second residence time) was optimal for further screening.

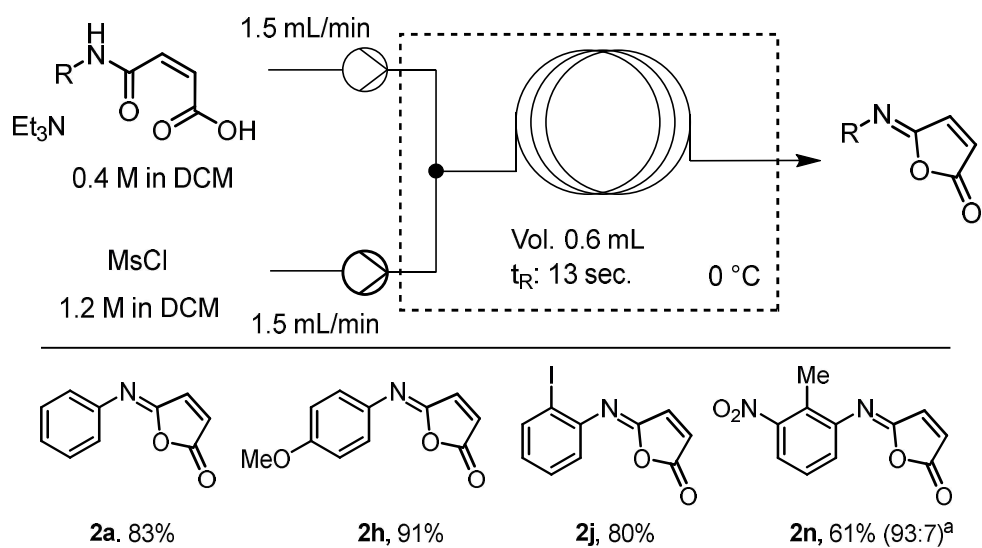
Table 6. Optimization of Protodecarboxylation In Flow

Entry	Et ₃ N (equiv.)	MsCl (equiv.)	Flow rate (mL/min.)	RT (sec)	2j (%)
1	2.0	1.0	3	13	75
2	2.0	2.0	3	13	79
3	2.0	3.0	3	13	80
4	3.0	1.0	3	13	67
5	3.0	2.0	3	13	75
6	3.0	3.0	3	13	88
7	3.0	3.0	1	36	87
8	3.0	3.0	6	6	83
9	3.0	3.0	12	3	83
10	3.0	3.0	18	2	83
11^a	3.0	3.0	6	13	89

Reaction conditions (unless otherwise noted): reactions were carried out with substrate **1j** (1.0 equiv.) in DCM (0.4 M), flow rates for both the syringe pumps were same in all cases (each at half the indicated flow rate in the table) and reactor length was 3 m (0.6 mL volume, 0.2 M reaction concentration for **1j**); Yields determined using quantitative ¹H NMR with 1,3,5-trimethoxybenzene (TMB) as internal standard. [a] reactor length of 6 m (1.2 mL volume).

Under the optimized flow reaction conditions, some maleamic acid derivatives were examined for comparison with the batch reactions (Table 7). The reactions proceeded as anticipated, to generate products **2a**, **2h**, **2j**, and **2n** in 83%, 91%, 80%, and 61% yields, respectively, which is in alignment with the batch reaction yields. These results indicate that the dehydration process works similarly well, and the reaction time can be reduced significantly under the continuous flow reaction protocol.

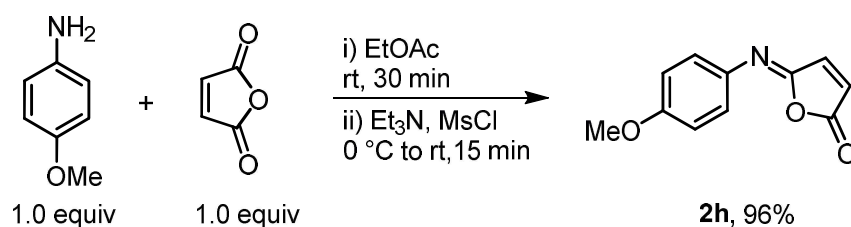
Table 7. Flow Synthesis of Select Substrates



Unless otherwise stated, reactions were performed at 0 °C using maleamic acid **1** (1.0 equiv, 0.2 mmol, 0.4 M solution in DCM), MsCl (3.0 equiv, 0.6 mmol, 1.2 M solution in DCM), and Et_3N (3.0 equiv, 0.6 mmol) with both syringe pumps set at a flow rates of 1.5 mL/min. All yields determined via product isolation. [a] combined yield and ratio (shown in parenthesis) of an inseparable mixture of isomaleimide and maleimide mixture.

With the compatibility of the reaction conditions for both the syntheses of maleamic acids and their subsequent dehydration to isomaleimides, an obligatory two-step, one-flask synthesis of isomaleimide from an aniline and maleic anhydride was attempted (Scheme 2). The treatment of a 1:1 mixture of *p*-anisidine and maleic anhydride, followed by addition of Et₃N and MsCl gave product **2h** in an excellent (96%) yield. This process converts simple, commodity chemicals into isomaleimides, a heterocycle with untapped potential.

Scheme 12. One-Flask Synthesis of Isomaleimides From Aniline



In conclusion, a simple and efficient synthesis of isomaleimides by dehydration of maleamic acid using methanesulfonyl chloride as a dehydrating agent is described. This process was also demonstrated in the flow synthesis of the isomaleimides with comparable yields to batch synthesis while requiring substantially shorter reaction times. A variety of substrates are found to be tolerable under the reported protocol. Further studies on the applications of isomaleimides are currently under investigation.

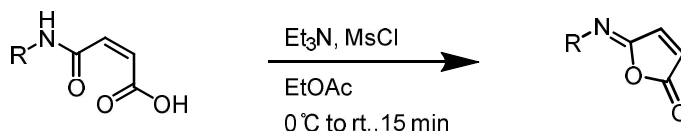
Experimental

GENERAL INFORMATION

^1H NMR and ^{13}C NMR spectra were recorded in DMSO- d_6 or CDCl_3 on JEOL ECS 400 MHz and/or JEOL ECA 500 MHz NMR spectrometers. Chemical shifts (δ) and coupling constants (J) are given in parts per million (ppm) and in hertz (Hz), respectively. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sextet = sx, dd = doublet of doublets, tt = triplet of triplets, m = multiplet. High-resolution mass spectrometry data were recorded on a Synapt G2 HDMS (q-TOF with ion mobility). Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates (60 F254) using UV light as the visualizing agent. Purifications by flash column chromatography were carried out using SiliaFlash® P60 silica gel with a hexane–EtOAc solvent mixture. Maleamic acids (**1**) were prepared according to the literature procedure.¹⁴ Unless otherwise noted, all reagents were purchased from commercial sources and used without further purification.

GENERAL PROCEDURE FOR THE SYNTHESIS OF ISOMALEIMIDES

Scheme 13. General Isomaleimide Synthesis



Maleamic acid **1** (0.2 mmol) was taken into a 7 mL vial and EtOAc (1 mL, 0.2 M) was added. The mixture was cooled down to $0\text{ }^\circ\text{C}$ and Et_3N (0.6 mmol, 3.0 equiv.) was added dropwise, and the mixture was stirred for 5 min resulting in a clear solution. MsCl (0.6 mmol, 3.0 equiv.) was added dropwise at $0\text{ }^\circ\text{C}$ and the solution was warmed to room temperature. After 15 min, the reaction mixture was cooled to $0\text{ }^\circ\text{C}$ and quenched with 5% aq. NaOH solution ($\sim 5\text{ mL}$). The reaction mixture was immediately extracted with EtOAc and the organic layer was washed with brine, dried over MgSO_4 , and concentrated under vacuum. The crude product was purified by silica gel column chromatography and the product (**2**) was separated using hexane–EtOAc as eluent.

GENERAL PROCEDURE FOR FLOW REACTION OPTIMIZATION

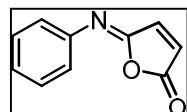
To a 5 mL volumetric flask maleamic acid **1** (2.00 mmol) and DCM (1 mL) were sequentially added. The solution is cooled to 0 °C in an ice bath and triethylamine (6 mmol, 3.0 equiv) is added. The flask is warmed to room temperature and diluted to a total volume of 5 mL using DCM (0.4 M). To a separate 5 mL volumetric flask is added methanesulfonyl chloride (6 mmol, 3.0 equiv) and DCM to 5 mL total volume (1.2 M). These two solutions are taken into separate syringes and loaded onto syringe pumps. Using the system shown in Scheme 14 and described in our website,¹⁶ both syringe pumps are initiated at 1.5 mL/min and passed through a 3 m (0.6 mL) reactor coil submerged in an ice bath. After 35 seconds, a reaction sample is collected for 20 sec (allowing 0.5 mL (0.2 mmol) of starting material solution passed through the flow system) into collection vial containing 5% aq. NaOH solution (~ 5 mL) for quenching and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane-EtOAc as eluent to give isomaleimides.

Scheme 14. Flow Reaction Setup



SPECTROSCOPIC DATA

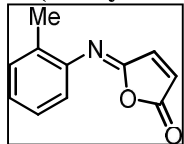
5-(phenylimino)furan-2(5H)-one (2a).^{15a} According to general procedure, **2a** was obtained in



85% (29.5 mg) yield as pale yellow solid (*syn* and *anti*-ratio, 90:10); ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.35 (m, 5H), 7.27 – 7.21 (m, 1H), 6.67 (d, J = 5.5

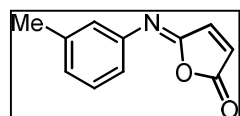
Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.3, 150.2, 143.5, 143.3, 129.1, 128.0, 127.5, 125.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_8\text{NO}_2$ 174.0555, found 174.0557.

5-(*o*-tolylimino)furan-2(5*H*)-one (2b).^{15b} According to general procedure, **2b** was obtained in



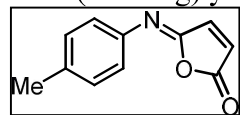
88% (33.0 mg) yield as yellow solid (*syn* and *anti*-ratio, 85:15); ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, J = 5.6 Hz, 1H), 7.28 – 7.07 (m, 4H), 6.70 (d, J = 5.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.3, 150.0, 142.8 (2C), 132.6, 130.6, 128.4, 126.8, 126.3, 122.3, 18.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{10}\text{NO}_2$ 188.0711, found 188.0710.

5-(*m*-tolylimino)furan-2(5*H*)-one (2c). According to general procedure, **2c** was obtained in



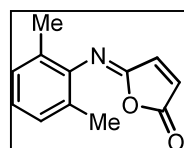
92% (34.5 mg) yield as yellow solid (*syn* and *anti*-ratio, 90:10); ^1H NMR (400 MHz, CDCl_3) δ 7.37 (d, J = 5.6 Hz, 1H), 7.24–7.18 (m, 3H), 7.05 (d, J = 8.3 Hz, 1H), 6.66 (d, J = 5.6 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.4, 150.0, 143.5, 143.3, 138.9, 128.9, 128.3, 127.9, 125.7, 122.2, 21.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{10}\text{NO}_2$ 188.0711, found 188.0709.

5-(*p*-tolylimino)furan-2(5*H*)-one (2d).^{15b} According to general procedure, **2d** was obtained in 86% (32.2 mg) yield as yellow solid (*syn* and *anti*-ratio, 92:8); ^1H NMR (400 MHz, CDCl_3) δ



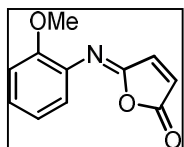
7.40 – 7.33 (m, 3H), 7.18 (d, J = 8.5 Hz, 2H), 6.64 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.5, 149.5, 143.4, 140.9, 138.0, 129.7, 127.5, 125.8, 21.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{10}\text{NO}_2$ 188.0711, found 188.0709.

5-((2,6-dimethylphenyl)imino)furan-2(5*H*)-one (2e). According to general procedure, **2e** was



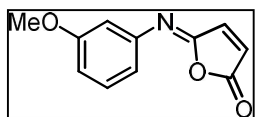
obtained in 98% (39.5 mg) yield as yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, J = 5.6 Hz, 1H), 7.50 – 6.96 (m, 3H), 6.70 (d, J = 5.6 Hz, 1H), 2.29 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.5, 150.6, 143.4, 141.7, 129.6, 127.9, 127.0, 124.9, 18.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{12}\text{H}_{12}\text{NO}_2$ 202.0868, found 202.0868.

5-((2-methoxyphenyl)imino)furan-2(5H)-one (2f).^{15b} According to general procedure, **2f** was



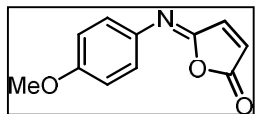
obtained in 92% (37.3 mg) yield as yellow solid (*syn* and *anti*-ratio, 89:11); ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 5.5 Hz, 1H), 7.33 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.24 – 7.15 (m, 1H), 6.99 – 6.90 (m, 2H), 6.66 (d, *J* = 5.5 Hz, 1H), 3.87 (s, 3H); ¹³C NMR (101 MHz CDCl₃) δ 167.2, 152.9, 151.0, 143.1, 133.0, 128.3, 128.1, 124.2, 120.7, 111.5, 55.9; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd. for C₁₁H₁₀NO₃ 204.066, found 204.0659.

5-((3-methoxyphenyl)imino)furan-2(5H)-one (2g). According to general procedure, **2g** was



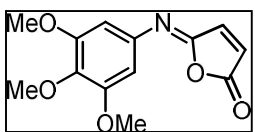
obtained in 90% (36.5 mg) yield as yellow solid (*syn* and *anti*-ratio, 90:10); ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J* = 5.5 Hz, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 7.00 – 6.95 (m, 1H), 6.91 (t, *J* = 2.2 Hz, 1H), 6.80 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.67 (d, *J* = 5.5 Hz, 1H), 3.80 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 167.1, 160.0, 150.4, 144.7, 143.2, 129.7, 128.2, 117.4, 113.3, 110.5, 55.4; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd. for C₁₁H₁₀NO₃ 204.066, found 204.0659.

5-((4-methoxyphenyl)imino)furan-2(5H)-one (2h).^{15b} According to general procedure, **2h** was



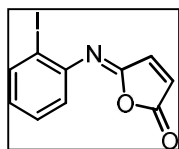
obtained in 94% (38.2 mg) yield as yellow solid (*syn* and *anti*-ratio, 96:4); ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 5.5 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.60 (d, *J* = 5.5 Hz, 1H), 3.81 (s, 3H); ¹³C NMR (101 MHz CDCl₃) δ 167.7, 159.4, 148.5, 143.6, 136.5, 128.5, 126.7, 114.3, 55.5; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd. for C₁₁H₁₀NO₃ 204.066, found 204.0662.

5-((3,4,5-trimethoxyphenyl)imino)furan-2(5H)-one (2i). According to general procedure, **2i**



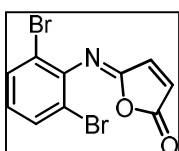
was obtained in 88% (46.3 mg) yield as yellow solid (*syn* and *anti*-ratio, 93:7); ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, *J* = 5.5 Hz, 1H), 6.74 (s, 2H), 6.64 (d, *J* = 5.5 Hz, 1H), 3.84 (s, 6H), 3.84 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 167.3, 153.2, 149.6, 143.4, 139.1, 137.8, 127.5, 103.6, 61.1, 56.2; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd. for C₁₃H₁₄NO₅ 264.0872, found 264.0874.

5-((2-iodophenyl)imino)furan-2(5H)-one (2j). According to general procedure, **2j** was obtained



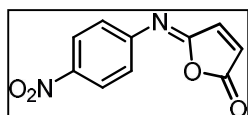
in 86% (51.4 mg) yield as yellow solid (*syn* and *anti*-ratio, 90:10); ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, J = 6.7 Hz, 1H), 7.49 (d, J = 5.6 Hz, 1H), 7.34 (t, J = 8.3 Hz, 1H), 7.26 – 7.19 (m, 1H), 6.91 (t, J = 8.4 Hz, 1H), 6.73 (d, J = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.6, 151.4, 145.8, 142.8, 139.3, 129.0, 128.9, 127.9, 122.6, 94.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_7\text{INO}_2$ 299.9521, found 299.9519.

5-((2,6-dibromophenyl)imino)furan-2(5H)-one (2k). According to general procedure, **2k** was



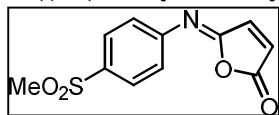
obtained in 81% (53.6 mg) yield as yellow solid (*syn* and *anti*-ratio, 91:9); ^1H NMR (400 MHz, CDCl_3) δ 7.53 (m, 3H), 6.90 (t, J = 8.1 Hz, 1H), 6.78 (d, J = 5.6 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.52, 153.72, 143.54, 141.64, 131.96, 130.61, 126.98, 114.51; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_6\text{Br}_2\text{NO}_2$ 329.8765, found 329.8760.

5-((4-nitrophenyl)imino)furan-2(5H)-one (2l).^{15a,15b} According to general procedure (reaction



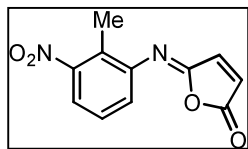
was quenched with sat. NaHCO_3), a combined yield of isomaleimide **2l** and maleimide **3l** mixture (ratio: 85:15) was obtained in 75% (32.5 mg) yield as yellow solid; **2l**. ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, J = 8.9 Hz, 2H), 7.44 (d, J = 5.5 Hz, 1H), 7.36 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 5.5 Hz, 1H); **3l**. ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, J = 9.1 Hz, 2H), 7.67 (d, J = 9.1 Hz, 2H), 6.92 (s, 2H); (**2l** + **3l**) ^{13}C NMR (101 MHz, CDCl_3) δ 168.6, 166.0, 152.3, 149.6, 145.8, 142.7, 137.1, 134.7, 129.6, 125.6, 124.7, 124.6, 124.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_7\text{N}_2\text{O}_4$ 219.0406, found 219.0404.

5-((4-(methylsulfonyl)phenyl)imino)furan-2(5H)-one (2m). According to general procedure, a



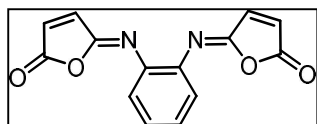
combined yield of isomaleimide **2m** and maleimide **3m** mixture (ratio: 88:12) was obtained in 62% (31.2 mg) yield as pale yellow solid; **2m**. ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 5.6 Hz, 1H), 7.38 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 5.6 Hz, 1H), 3.06 (s, 3H). **3m**. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 6.91 (s, 2H), 3.07 (s, 3H); (**2m** + **3m**) ^{13}C NMR (101 MHz, CDCl_3) δ 168.7, 166.1, 152.2, 148.7, 142.7, 138.0, 134.6, 129.5, 128.5, 126.0, 124.3, 44.7, 44.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{10}\text{NO}_4\text{S}$ 252.0331, found 252.0327.

5-((2-methyl-3-nitrophenyl)imino)furan-2(5H)-one (2n). According to general procedure, a



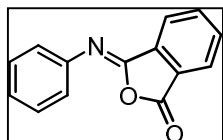
combined yield of isomaleimide **2n** and maleimide **3n** mixture (ratio: 95:5) was obtained in 65% (30.2 mg) yield as yellow solid; **2n**. ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 5.6 Hz, 1H), 7.38 – 7.27 (m, 2H), 6.78 (d, J = 5.6 Hz, 1H), 2.42 (s, 3H); **2n**. ^{13}C NMR (101 MHz, CDCl_3) δ 166.3, 151.8, 144.8, 142.5, 129.4, 127.0, 126.5, 126.1, 121.9, 14.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_9\text{N}_2\text{O}_4$ 233.0562, found 233.0561.

5,5'-(1,2-phenylenebis(azaneylylidene))bis(furan-2(5H)-one) (2o).^{15b} According to general



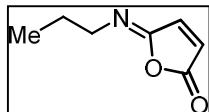
procedure (twice as much Et_3N and MsCl was used), **2o** was obtained in 73% (42.5 mg) yield as yellow solid (*syn* and *anti*-ratio, 84:16); ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, J = 5.5 Hz, 2H), 7.34 (m, 2H), 7.24 (m, 2H), 6.68 (d, J = 5.6 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.8, 151.5, 142.8, 137.9, 128.6, 127.3, 123.6; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_4$ 269.0562, found 269.0561.

3-(phenylimino)isobenzofuran-1(3H)-one (2p).^{15c} According to general procedure, **2p** was



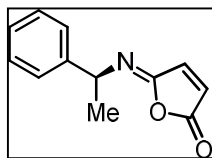
obtained in 73% (32.5 mg) yield as white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 7.7 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.45 – 7.34 (m, 4H), 7.24 – 7.17 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 165.0, 147.1, 143.9, 137.1, 135.5, 133.2, 129.0, 127.8, 126.5, 125.4, 124.5, 123.8; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{10}\text{NO}_2$ 224.0706, found 224.0705.

5-(propylimino)furan-2(5H)-one (2q). According to general procedure, **2q** was obtained in



73% (20.3 mg) yield as colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.21 (d, J = 5.6 Hz, 1H), 6.60 (d, J = 5.6 Hz, 1H), 3.58 (t, J = 7.0 Hz, 2H), 1.68 (sx, J = 7.3 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.1, 151.9, 142.2, 128.5, 51.6, 23.7, 11.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_7\text{H}_{10}\text{NO}_2$ 140.0711, found 140.0710.

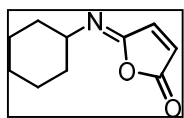
(S)-5-((1-phenylethyl)imino)furan-2(5H)-one (2r).^{15b} According to general procedure, **2r** was



obtained in 85% (34.2 mg) yield as white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.39 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.21 (m, 2H), 6.60 (d, *J* = 5.6 Hz, 1H), 5.18 (q, *J* = 6.6 Hz, 1H), 1.54 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 166.9, 151.0, 143.8, 142.6, 128.7, 128.6, 127.4, 126.7, 58.6,

24.2; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd. for C₁₂H₁₂NO₂ 202.0867, found 202.0868.

5-(cyclohexylimino)furan-2(5H)-one (2s).^{15d} According to general procedure, **2s** was obtained



in 92% (33.0 mg) yield as colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.19 (d, *J* = 6.4 Hz, 1H), 6.58 (d, *J* = 6.3 Hz, 1H), 3.82 (tt, *J* = 10.2, 3.5 Hz, 1H), 1.81 – 1.69 (m, 4H), 1.68 – 1.58 (m, 1H), 1.47 – 1.15 (m, 5H); ¹³C NMR (101 MHz,

CDCl₃) δ 167.2, 150.5, 142.5, 128.4, 58.4, 33.6, 25.5, 24.4; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd. for C₁₀H₁₄NO₂ 180.1019, found 180.1013.

REFERENCES

(1) (a) Meldal, M.; Diness, F., Recent Fascinating Aspects of the CuAAC Click Reaction. *Trends Chem.* **2020**, *2*, 569-584. (b) Haldón, E.; Nicasio, M. C.; Pérez, P. J., Copper-catalysed azide–alkyne cycloadditions (CuAAC): an update. *Org. Biomol. Chem.* **2015**, *13*, 9528-9550. (c) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K., Click Chemistry for Drug Development and Diverse Chemical–Biology Applications. *Chem. Rev.* **2013**, *113*, 4905-4979.

(2) (a) Tsou, K.-C.; Barnett, R. J.; Seligman, A. M., Preparation of Some N-(1-Naphthyl)-maleimides as Sulfhydryl Group Reagents. *J. Am. Chem. Soc.* **1955**, *77*, 4613-4616. (b) Ezzell, S. A.; Hansen, R. G.; Anderson, G. J. Isomaleimides and polymers derived therefrom. PCT Int. Appl. WO 9720832 A1, **1997**, 51. (c) Harwood, H. J.; Pyriadi, T. M. Use of acetyl chloride-triethylamine and acetic anhydride-triethylamine mixtures in the synthesis of isomaleimides from maleamic acids. *J. Org. Chem.* **1971**, *36*, 821-823. (d) Curtin, D. Y.; Miller, L. L. 1,3 Acyl Migrations in Unsaturated Triad (Allyloid) Systems. Rearrangements of N-(2,4-Dinitrophenyl)benzimidoyl Benzoates. *J. Am. Chem. Soc.* **1967**, *89*, 637-645. (e) Cotter, R. J.; Sauers, C. K.; Whelan, J. M. The Synthesis of N-Substituted Isomaleimides. *J. Org. Chem.* **1961**, *26*, 10-15.

(3) (a) Kirino, O.; Rubin, B.; Casida, J. E. N-Phenyl-maleimides, -isomaleimides and -maleamic Acids as Selective Herbicide Antidotes. *Agric. Biol. Chem.* **2014**, *49*, 267-268. (b) Conley, N. R.; Hung, R. J.; Willson, C. G. A New Synthetic Route to Authentic N-Substituted Aminomaleimides. *J. Org. Chem.* **2005**, *70*, 4553-4555. (c) Fruk, L.; Graham, D. The electronic effects on the formation of N-arylmaleimides and isomaleimides. *Heterocycles* **2003**, *60*, 2305-2313. (d) Nielsen, O.; Buchardt, O. Facile synthesis of reagents containing a terminal maleimido ligand linked to an active ester. *Synthesis* **1991**, 819-821. (e) Corrie, J. E. T.; Moore, M. H.; Wilson, G. D. Product diversity in cyclisations of maleamic acids: the imide–isoimide dichotomy. *J. Chem. Soc., Perkin Trans. 1* **1996**, 777-781.

(4) (a) Joseph-Nathan, P.; Mendoza, V.; García E. Aziridine induced isomerization of isomaleimides to maleimides. *Can. J. Chem.* **1974**, *52*, 129–131. (b) Rubinstein, H.; Parnarouskis, M.; Feuer, H. Reactions of 3-carboxyacryloylhydrazines. II. Acid-induced rearrangement of isomaleimides. *J. Org. Chem.* **1973**, *38*, 2166-2169. (c) Narita, M.; Akiyama,

M.; Okawara, M. The Dehydration of N-Benzyloxy and N-Hydroxymaleamic Acid and the Isomerization of N-Benzyloxyisomaleimide. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 437-441.

(5) (a) Dolci, E.; Froidevaux, V.; Joly-Duhamel, C.; Auvergne, R.; Boutevin, B.; Caillol, S. Maleimides As a Building Block for the Synthesis of High Performance Polymers. *Polym. Rev.* **2016**, *56*, 512-556. (b) Nanda, T.; Ravikumar, P. C. A Palladium-Catalyzed Cascade C–C Activation of Cyclopropanone and Carbonylative Amination: Easy Access to Highly Functionalized Maleimide Derivatives. *Org. Lett.* **2020**, *22*, 1368-1374. (c) Li, X.-R.; Chen, S.-Q.; Fan, J.; Li, C.-J.; Wang, X.; Liu, Z.-W.; Shi, X.-Y. Controllable Tandem [3+2] Cyclization of Aromatic Aldehydes with Maleimides: Rhodium(III)-Catalyzed Divergent Synthesis of Indane-Fused Pyrrolidine-2,5-dione. *Org. Lett.* **2020**, *22*, 8808-8813. (d) Uno, B. E.; Deibler, K. K.; Villa, C.; Raghuraman, A.; Scheidt, K. A. Conjugate Additions of Amines to Maleimides via Cooperative Catalysis. *Adv. Synth. Catal.* **2018**, *360*, 1719-1725. (e) Ravasco, J. M. J. M.; Faustino, H.; Trindade, A.; Gois, P. M. P. Bioconjugation with Maleimides: A Useful Tool for Chemical Biology. *Chem. Eur. J.* **2018**, *25*, 43-59. (f) Cunha, S.; Rodovalho, W.; Azevedo, N. R.; Mendonça, M. d. O.; Lariucci, C.; Vencato, I. The Michael Reaction of Enaminones with N-(*p*-tolyl)-maleimide: Synthesis and Structural Analysis of Succinimide-enaminones. *J. Braz. Chem. Soc.* **2002**, *13*, 629-634.

(6) (a) Anderson, N. H.; Ollis, W. D.; Thorpe, J. E.; Ward, A. D. Studies concerning the antibiotic actinonin. Part II. Total synthesis of actinonin and some structural analogues by the isomaleimide method. *J. Chem. Soc., Perkin Trans. 1* **1975**, *9*, 825-830. (b) Guevara, J. A.; Trujillo, J. G.; Quintana, D.; Jiménez, H. A.; Arellano, M. G.; Bahena, J. R.; Tamay, F.; Ciprés, F. J. Acetylcholinesterase inhibition by products generated in situ from the transformation of N-aryl isomaleimides. *Med. Chem. Res.* **2018**, *27*, 989-1003. (c) Sarannya, V.; Rishwana, S. S.; Mahalakshmy, R.; Mahendran, A. R.; Surender, R.; Vijayakumar, C. T. Synthesis and thermal studies of bis(isomaleimide)/bisphenol A and ortho novalac blends. *J. Elastomers Plast.* **2019**, *52*, 495-520.

(7) (a) Klimenkovs, I.; Bakis, E.; Priksane, A., Propanephosphonic Acid Anhydride–Mediated Cyclodehydration of Maleic Acid Monoamides. *Synth. Commun.* **2013**, *43*, 2634-2640. (b) Haval, K. P.; Mhaske, S. B.; Argade, N. P. Cyanuric chloride: decent dehydrating agent for an

exclusive and efficient synthesis of kinetically controlled isomaleimides. *Tetrahedron* **2006**, *62*, 937-942. (c) Oishi, T.; Fujimoto, M.; Yoshimoto, N.; Kimura, T. Anionic Polymerizations of N-Substituted Isomaleimide. *Polym. J.* **1989**, *21*, 655-659.

(8) (a) Al-Huniti, M. H.; Perez, M. A.; Garr, M. K.; Croatt, M. P., Palladium-Catalyzed Chemoselective Protodecarboxylation of Polyenoic Acids. *Org. Lett.* **2018**, *20*, 7375-7379. (b) Deiab, G. a. I. A.; Al-Huniti, M. H.; Hyatt, I. F. D.; Nagy, E. E.; Gettys, K. E.; Sayed, S. S.; Joliat, C. M.; Daniel, P. E.; Vummalaneni, R. M.; Morehead, A. T.; Sargent, A. L.; Croatt, M. P., Decarboxylative and dehydrative coupling of dienolic acids and pentadienyl alcohols to form 1,3,6,8-tetraenes. *Beilstein J. Org. Chem.* **2017**, *13*, 384-392. (c) Abu Deiab, G. a. I.; Croatt, M. P., Synthetic approaches to isocarbacyclin and analogues as potential neuroprotective agents against ischemic stroke. *Bioorg. Med. Chem.* **2019**, *27*, 338-342. (d) Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P., Sequential Pd(0)-, Rh(I)-, and Ru(II)-Catalyzed Reactions in a Nine-Step Synthesis of Clinprost. *Org. Lett.* **2013**, *15*, 586-589. (e) Al-Huniti, M. H.; Rivera-Chávez, J.; Colón, K. L.; Stanley, J. L.; Burdette, J. E.; Pearce, C. J.; Oberlies, N. H.; Croatt, M. P., Development and Utilization of a Palladium-Catalyzed Dehydration of Primary Amides to Form Nitriles. *Org. Lett.* **2018**, *20*, 6046-6050.

(9) (a) Kurita, K.; Suzuki, Y.; Enari, T.; Kikuchi, M.; Nishimura, S. I.; Ishii, S. Isoimides and polyisoimides: Facile preparation and quantitative isomerization. *J. Polym. Sci., Part A: Polym. Chem.* **1994**, *32*, 393-396. (b) Shield Wallace, J.; Tan, L.-S.; Arnold, F. E. Synthesis and characterization of aromatic polyisoimides derived from PMDA and para-diamines. An approach to in situ generated rigid-rod molecular composites. *Polymer* **1990**, *31*, 2411-2419.

(10) Burness, D. M.; Wilson, B. D. Gelatin compositions containing a bis(isomaleimide) hardener. US 3232763, **1966**.

(11) Kozyrev, A. N.; Zheng, G.; Lazarou, E.; Dougherty, T. J.; Smith, K. M.; Pandey, R. K. Syntheses of emeraldin and purpurin-18 analogs as target-specific photosensitizers for photodynamic therapy. *Tetrahedron Lett.* **1997**, *38*, 3335-3338.

(12) (a) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; Robert McElroy, C.; Sherwood, J., Tools and techniques for solvent selection: green

solvent selection guides. *Sustain. Chem. Processes* **2016**, *4*, 7. (b) Capello, C.; Fischer, U.; Hungerbühler, K., What is a green solvent? A comprehensive framework for the environmental assessment of solvents. *Green Chem.* **2007**, *9*, 927-934.

(13) Webb, D.; Jamison, T. F., Diisobutylaluminum Hydride Reductions Revitalized: A Fast, Robust, and Selective Continuous Flow System for Aldehyde Synthesis. *Org. Lett.* **2011**, *14*, 568-571.

(14) (a) Fruk, L.; Graham, D., The Electronic Effects on the Formation of N-Arylmaleimides and isomaleimides. *Heterocycles* **2003**, *60*, 2305-2313. (b) Jha, A.; Duffield, K. M.; Ness, M. R.; Ravoori, S.; Andrews, G.; Bhullar, K. S.; Rupasinghe, H. P. V.; Balzarini, J., Curcumin-inspired cytotoxic 3,5-bis(arylmethylene)-1-(N-(ortho-substituted aryl)maleamoyl)-4-piperidones: A novel group of topoisomerase II alpha inhibitors. *Bioorg. Med. Chem.* **2015**, *23*, 6404-6417.

(15) (a) Guevara, J. A.; Trujillo, J. G.; Quintana, D.; Jiménez, H. A.; Arellano, M. G.; Bahena, J. R.; Tamay, F.; Ciprés, F. J., Acetylcholinesterase inhibition by products generated in situ from the transformation of N-arylisomaleimides. *Med. Chem. Res.* **2017**, *27*, 989-1003. (b) Haval, K. P.; Mhaske, S. B.; Argade, N. P., Cyanuric chloride: decent dehydrating agent for an exclusive and efficient synthesis of kinetically controlled isomaleimides. *Tetrahedron* **2006**, *62*, 937-942. (c) Guirado, A.; Zapata, A.; Carmen Ramírez de Arellano, M., The reaction of phthalidylidene dichloride with primary amines. Synthesis and X-ray molecular structure of N-substituted phthalisoimides. *Tetrahedron* **1997**, *53*, 5305-5324. (d) Klimenkovs, I.; Bakis, E.; Priksane, A., Propanephosphonic Acid Anhydride-Mediated Cyclodehydration of Maleic Acid Monoamides. *Synth. Commun.* **2013**, *43*, 2634-2640.

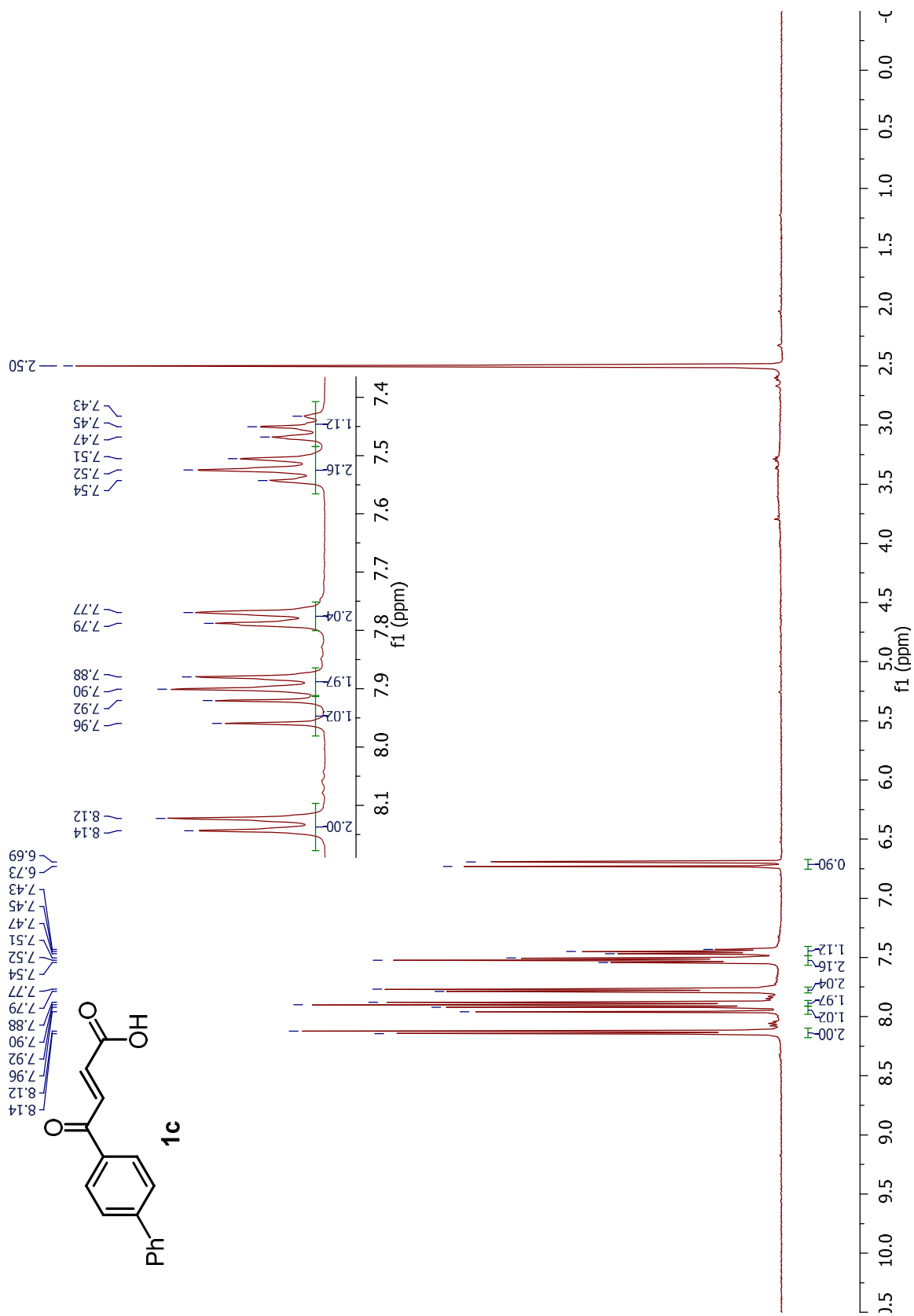
(16) <https://chem.uncg.edu/croatt/flow-chemistry/>

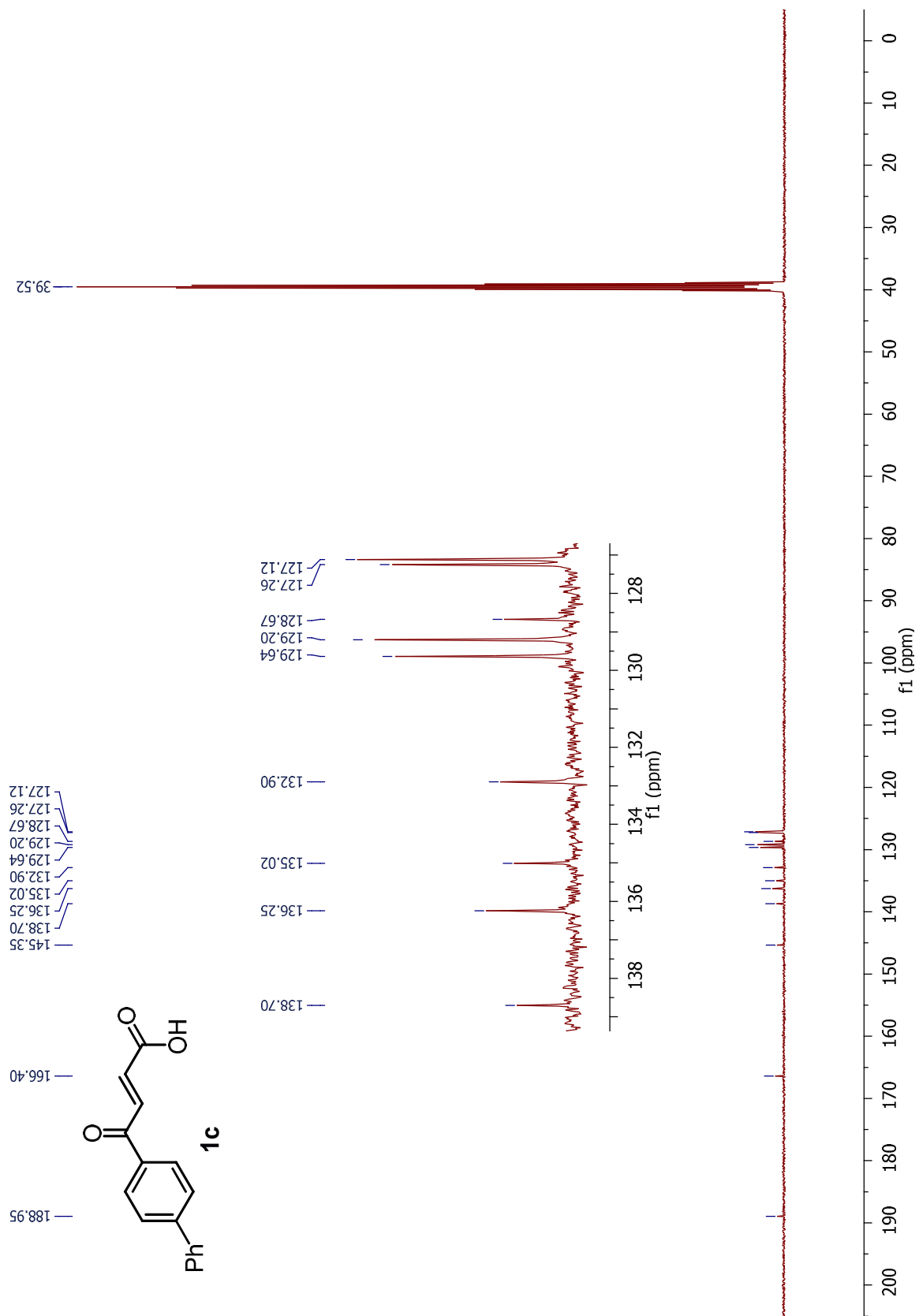
CHAPTER IV: CONCLUSION

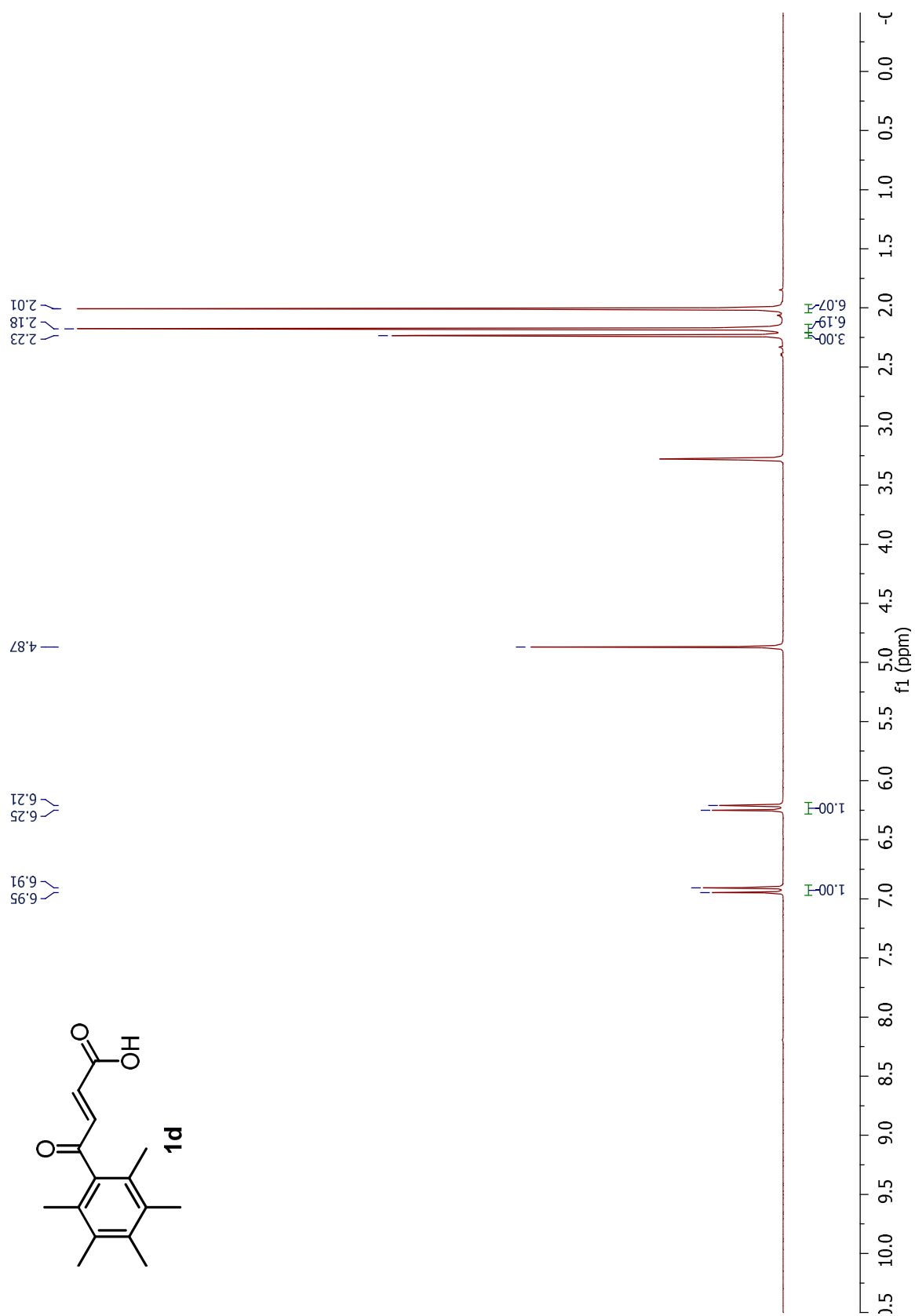
The advancement of the Croatt group's protodecarboxylation methodology is described. This novel methodology allows for the synthesis of terminal enone moieties from readily accessible β -keto acrylic acids. In comparison to other methodologies, this method can facilitate protodecarboxylation under notably milder conditions. Another unique component of this protodecarboxylation is its applicability to aliphatic β -keto acrylic acids.

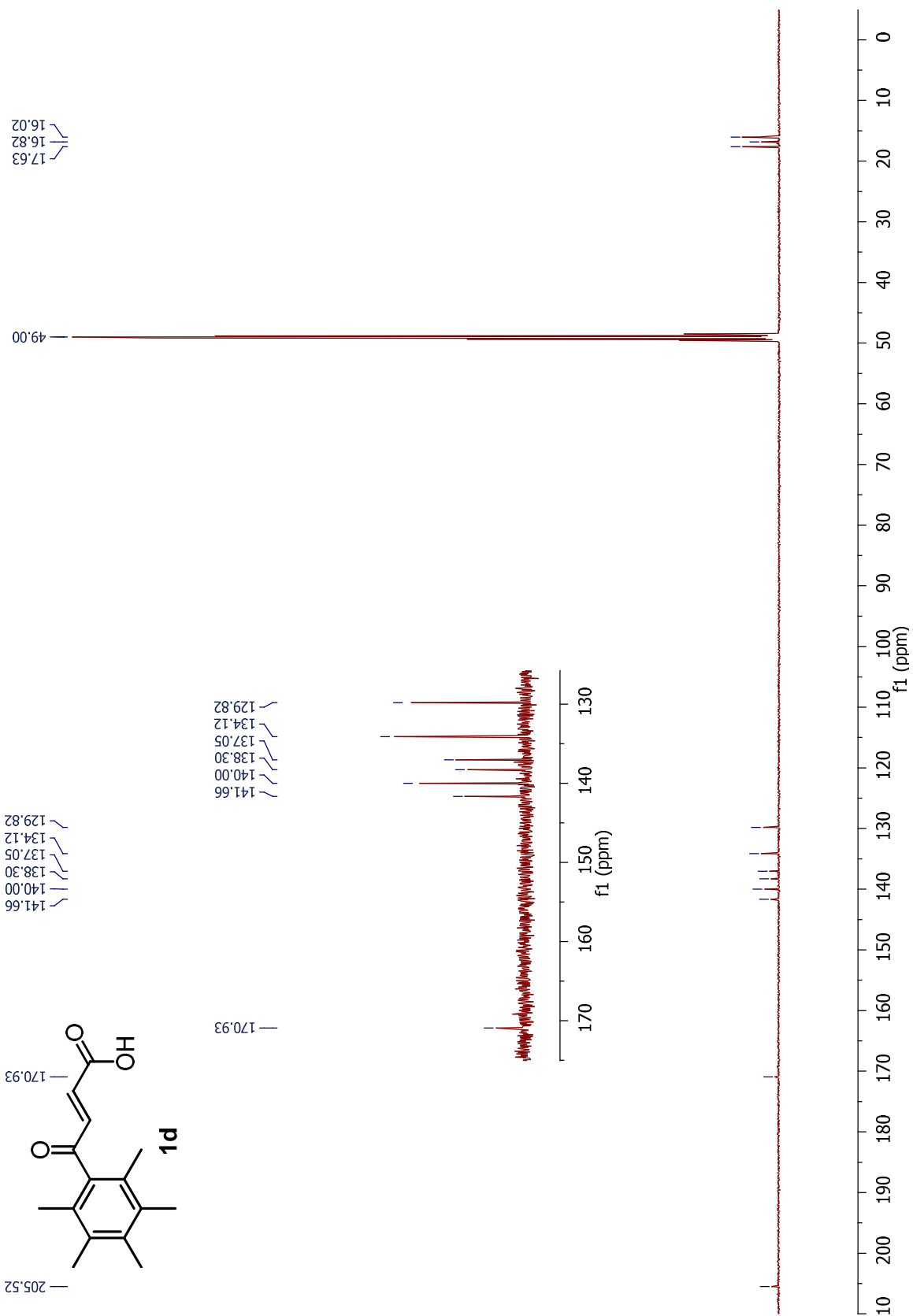
Additionally, the development of novel conditions for the synthesis of isomaleimides is described. Compared to other dehydrating agents commonly used for this transformation, this method's use of methane sulfonyl chloride provides a unique advantage, as showcased in its notably short reaction times, and low reaction temperatures. Flow chemistry experiments granted the ability to assess *how fast* the reaction is. Therein it was found that with a residence time of merely 2 seconds a yield of 83% was attained.

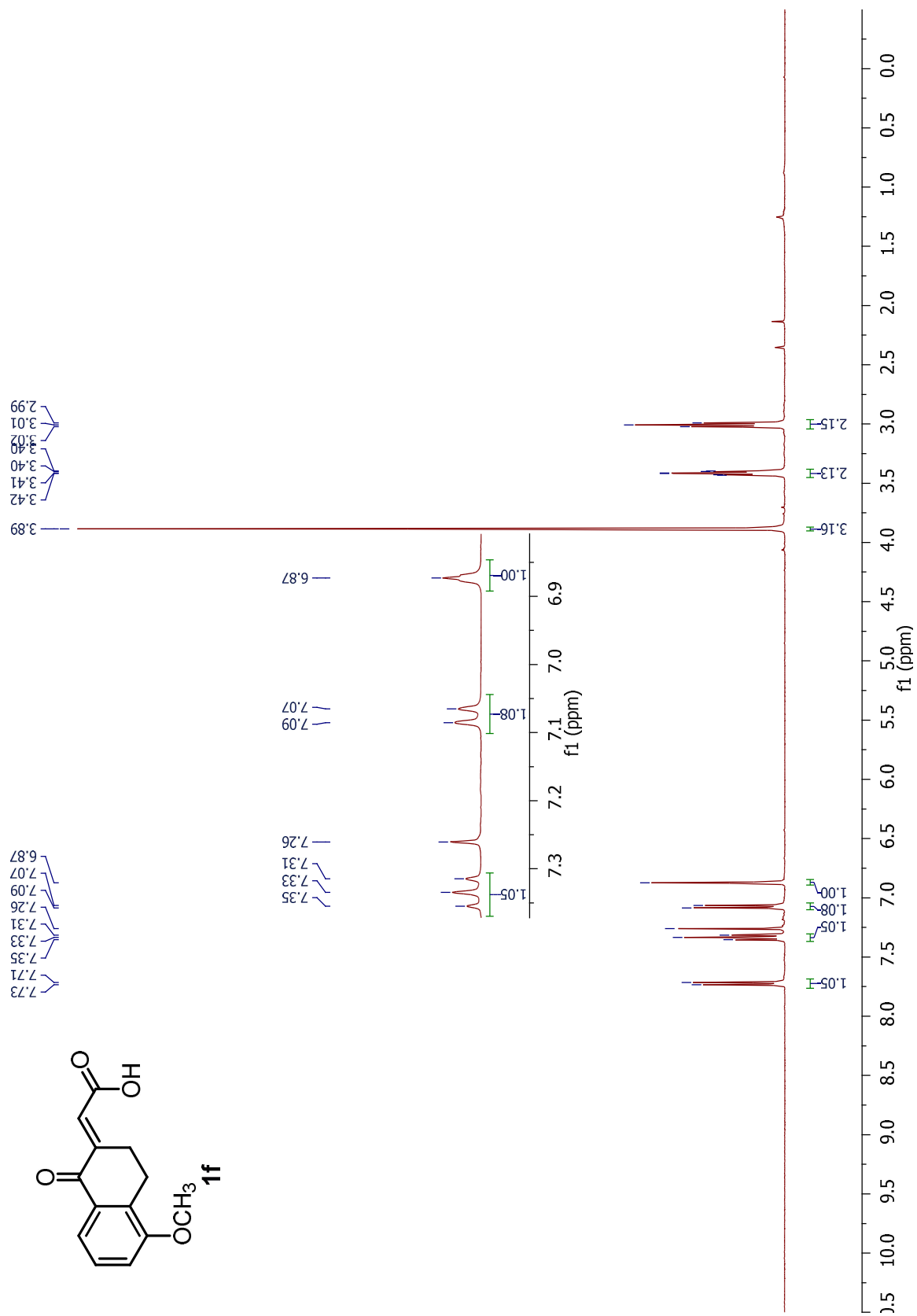
APPENDIX A: PROTODECARBOXYLATION - NMR SPECTRA

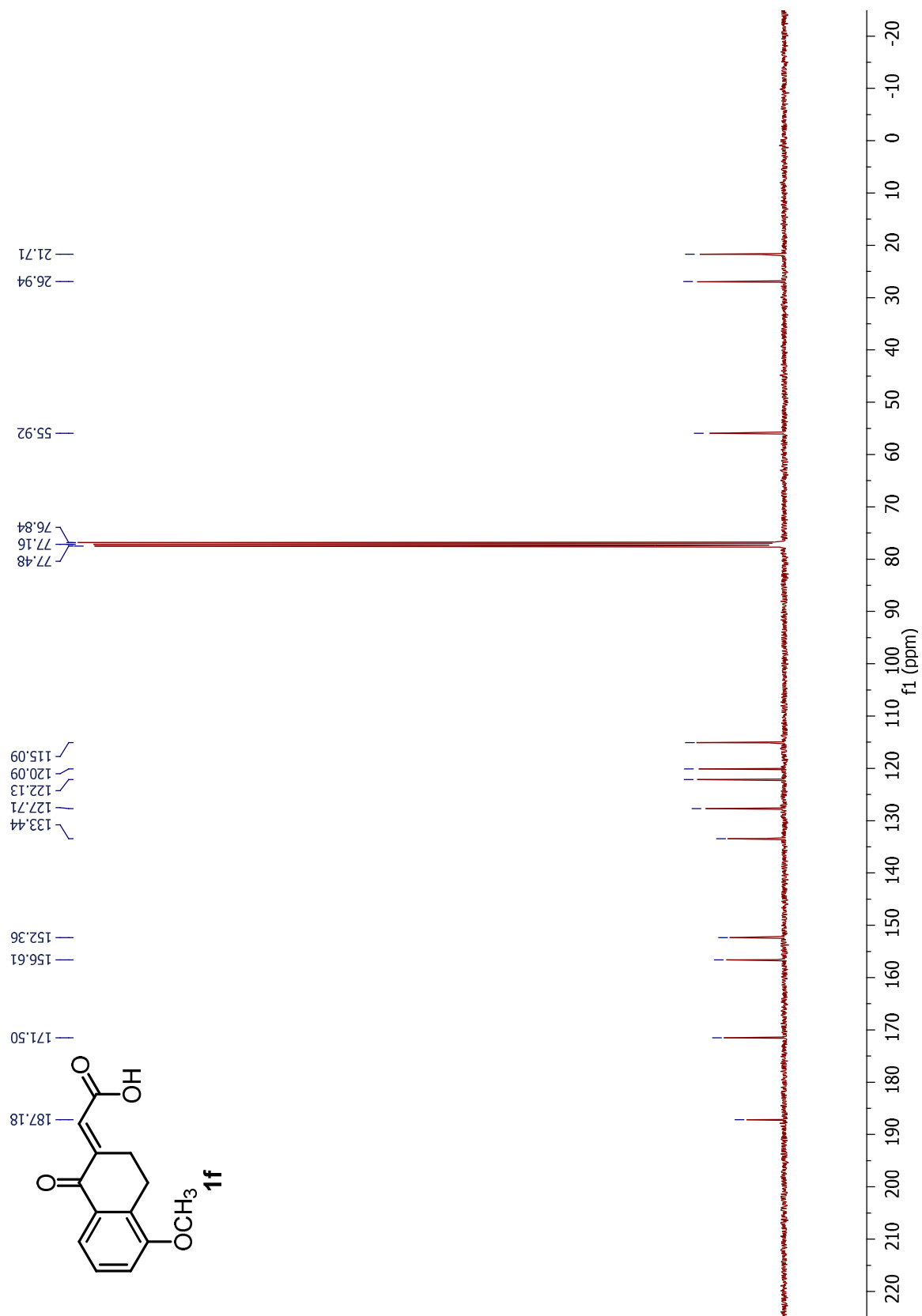


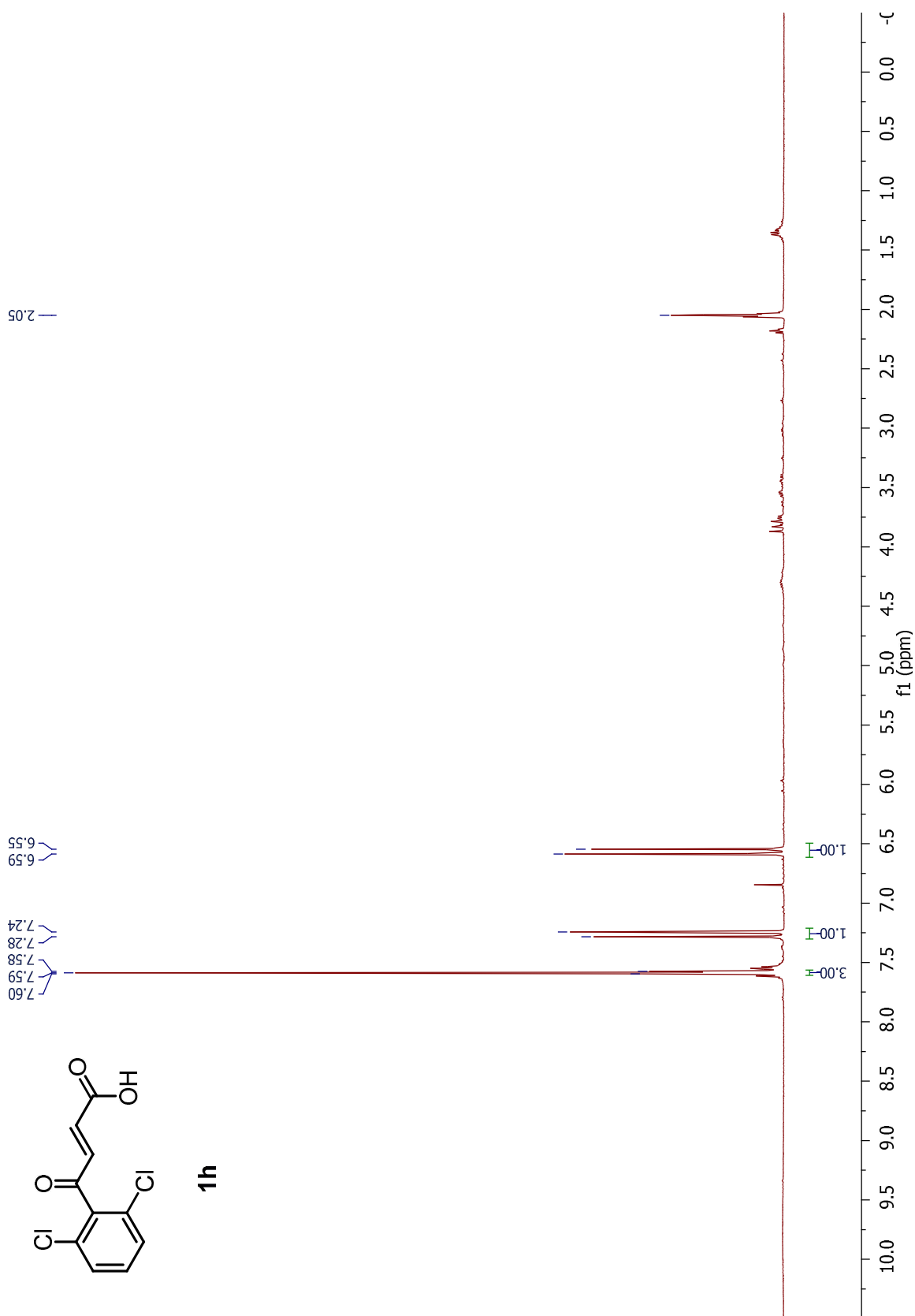


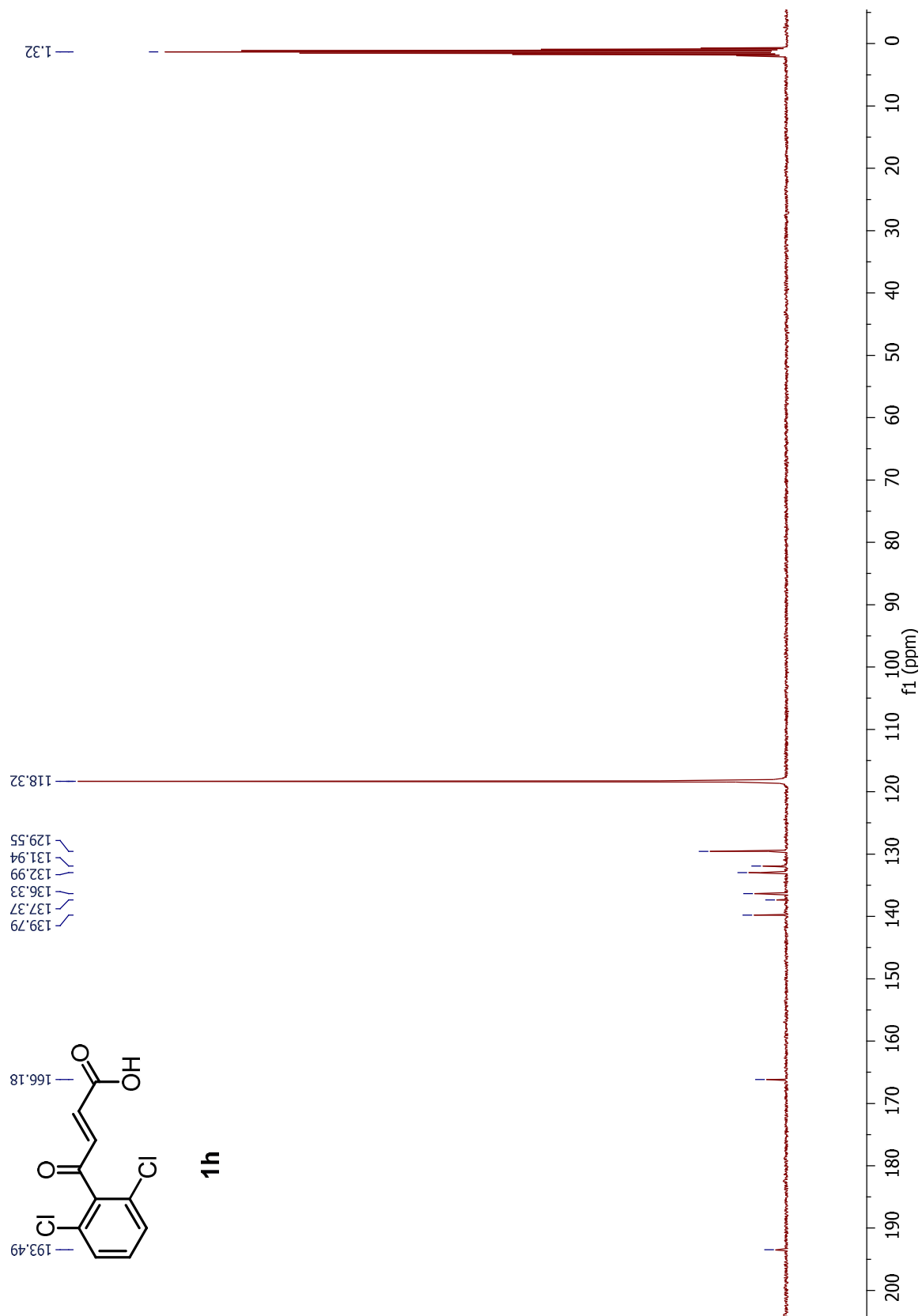


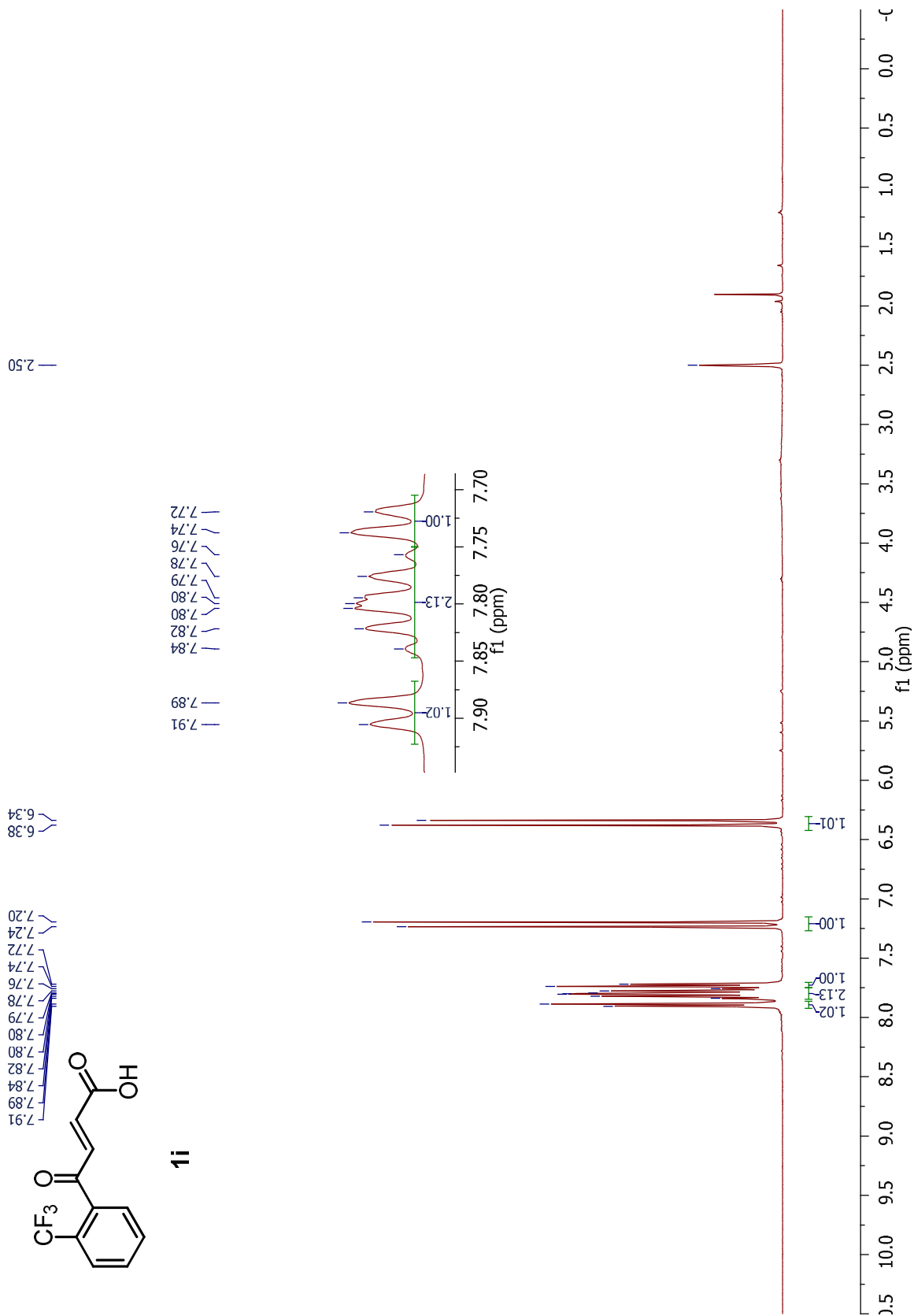


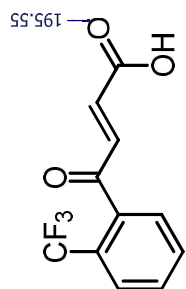




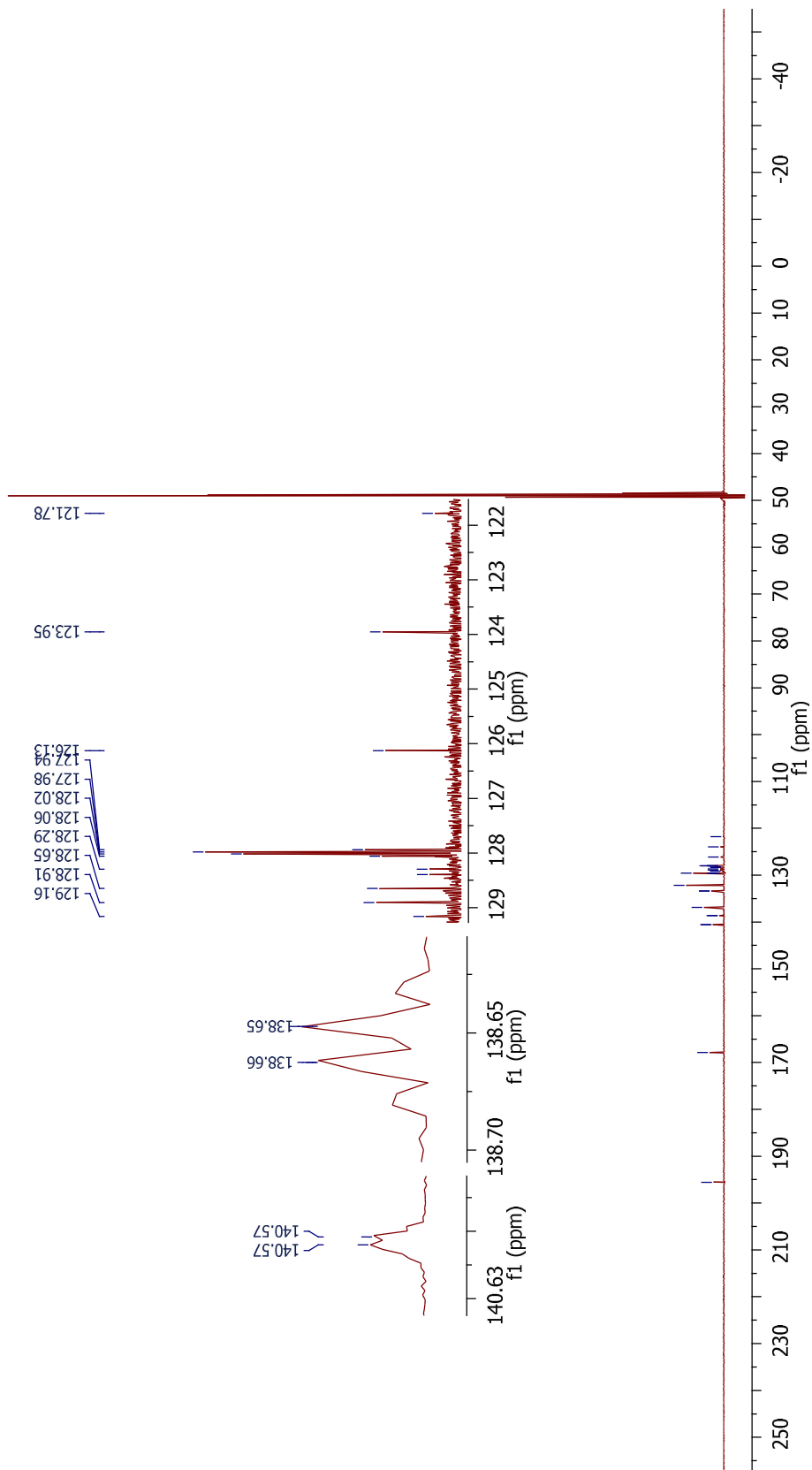
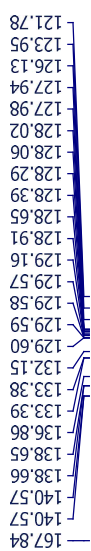


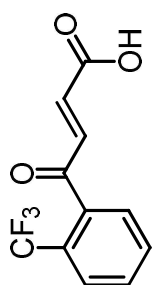




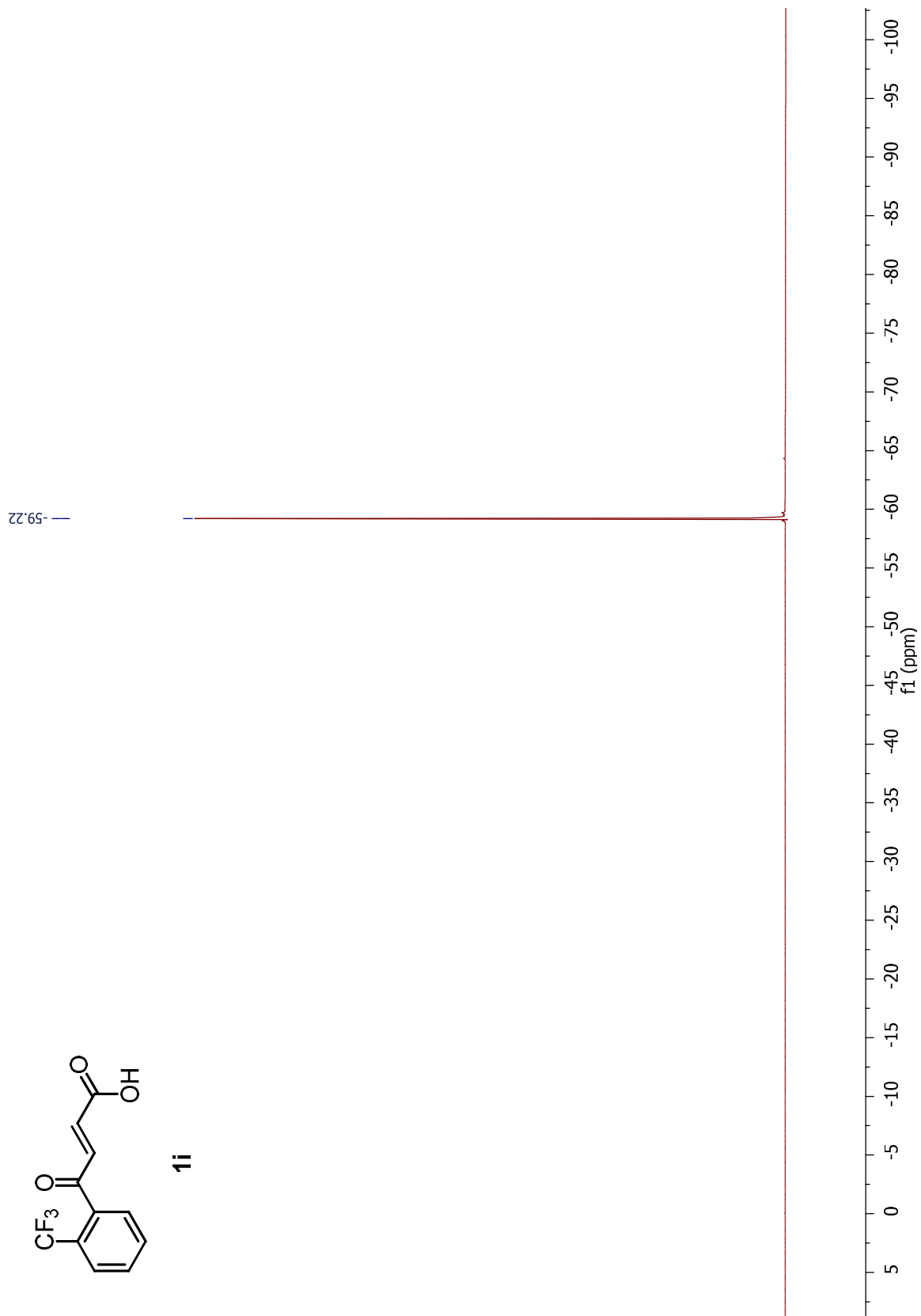


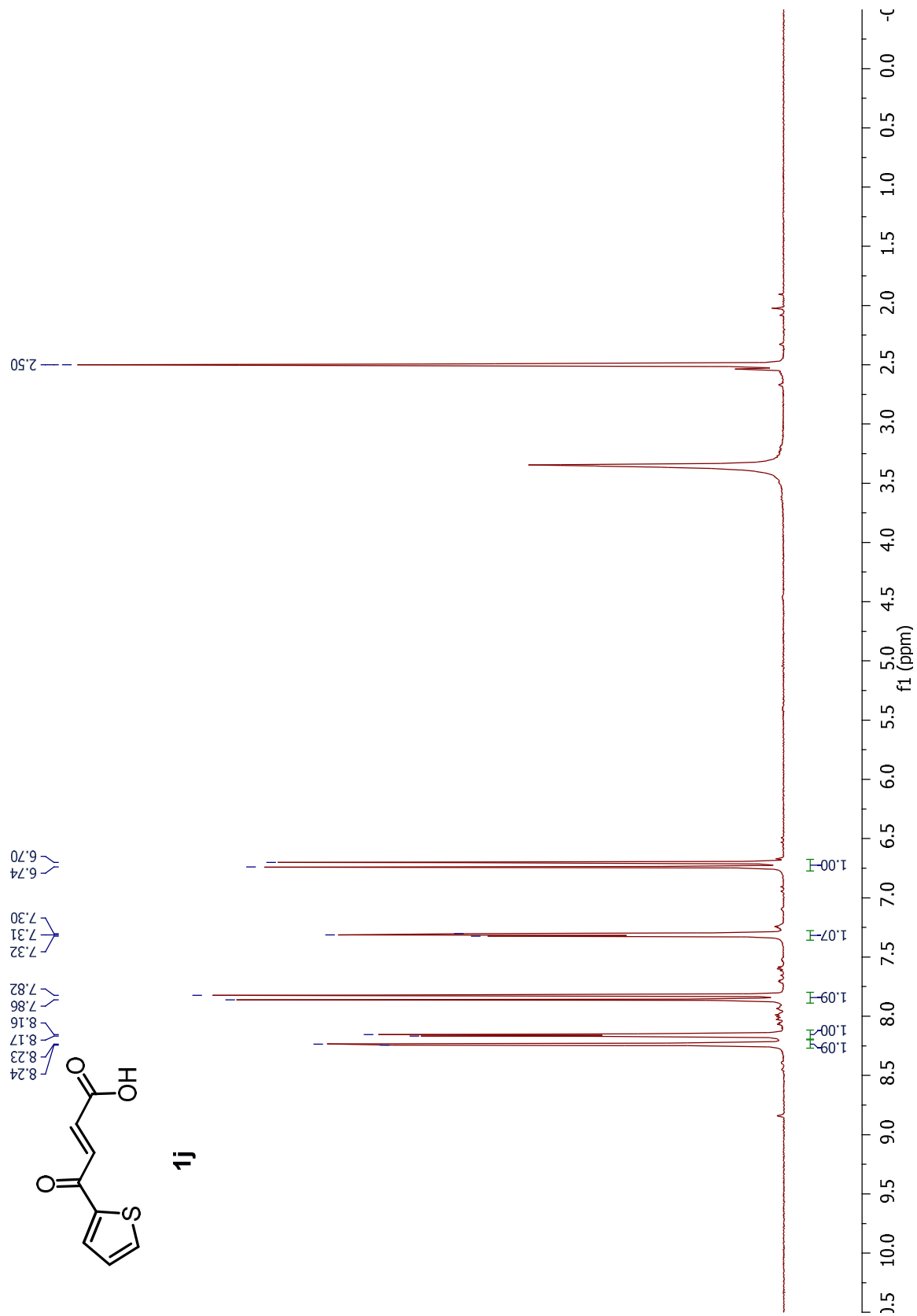
1i

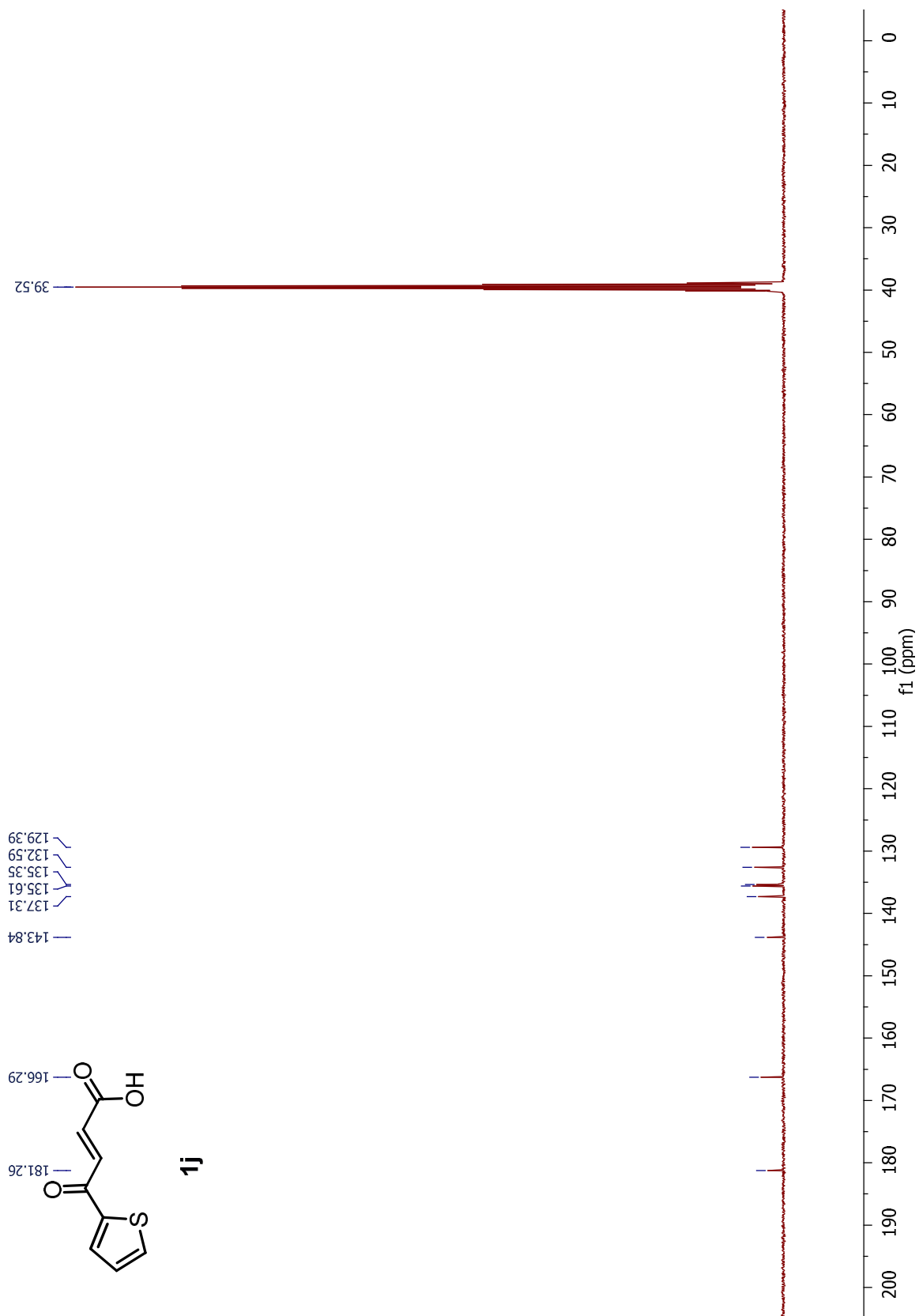


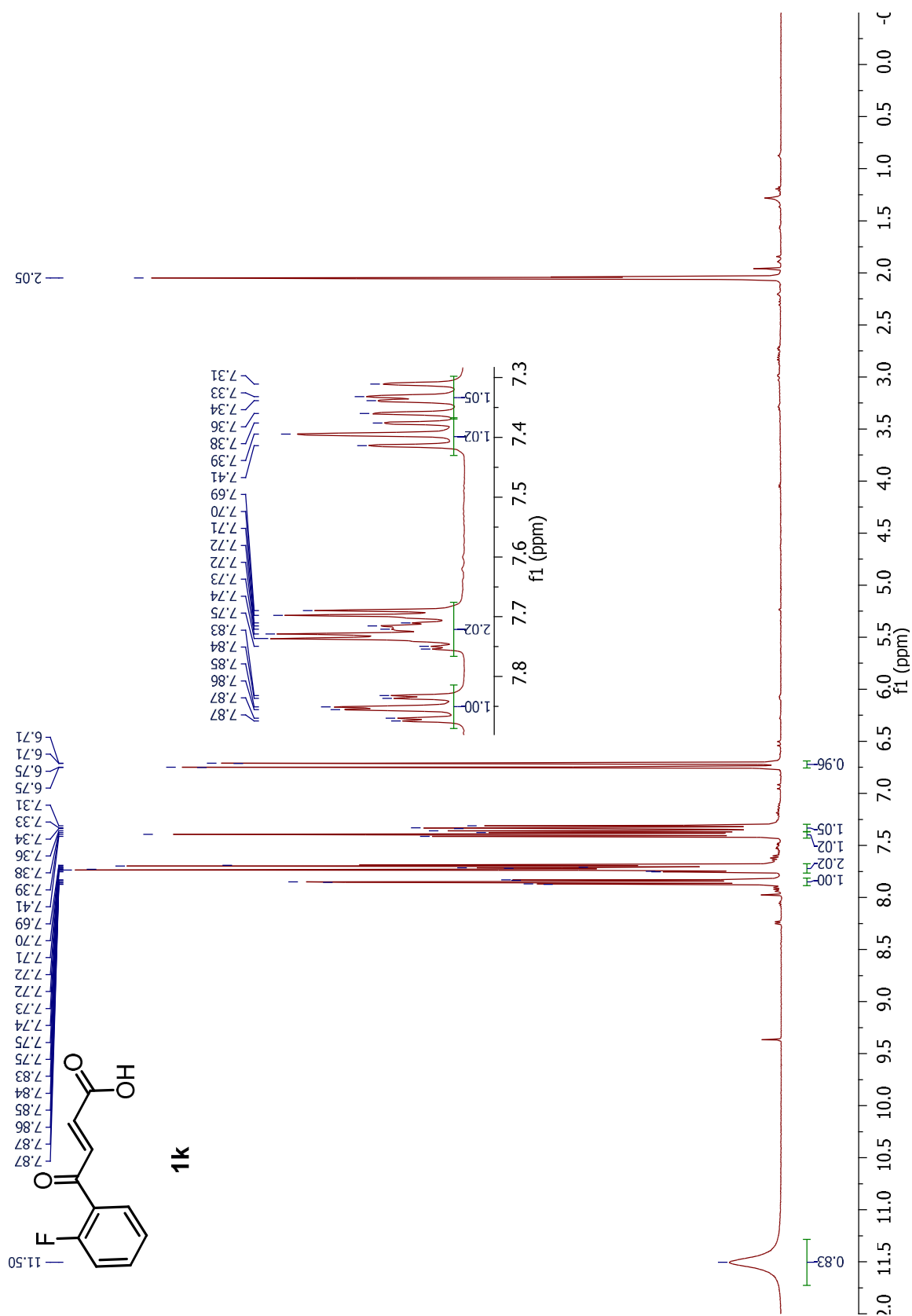


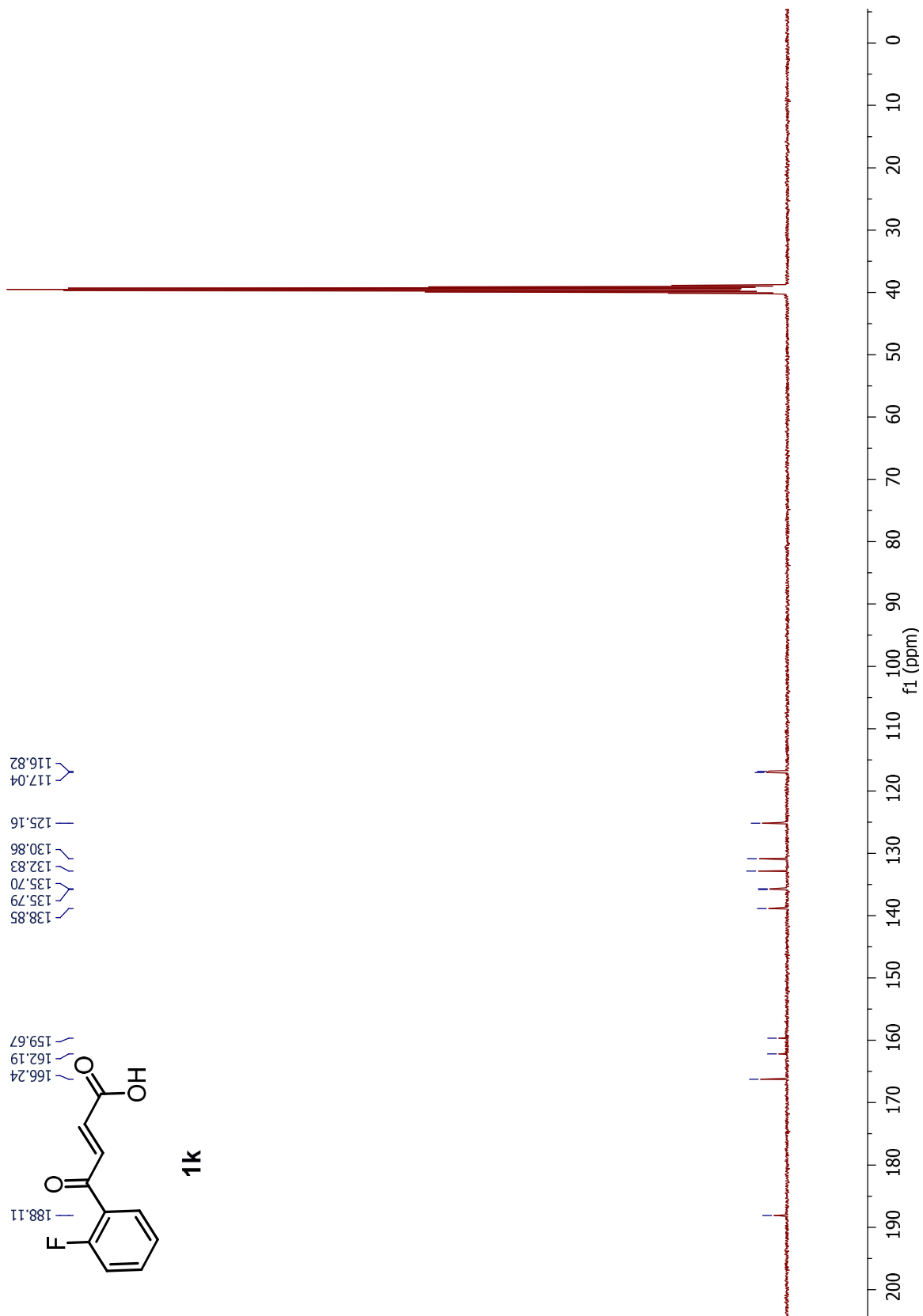
1i

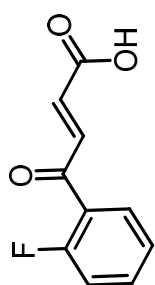




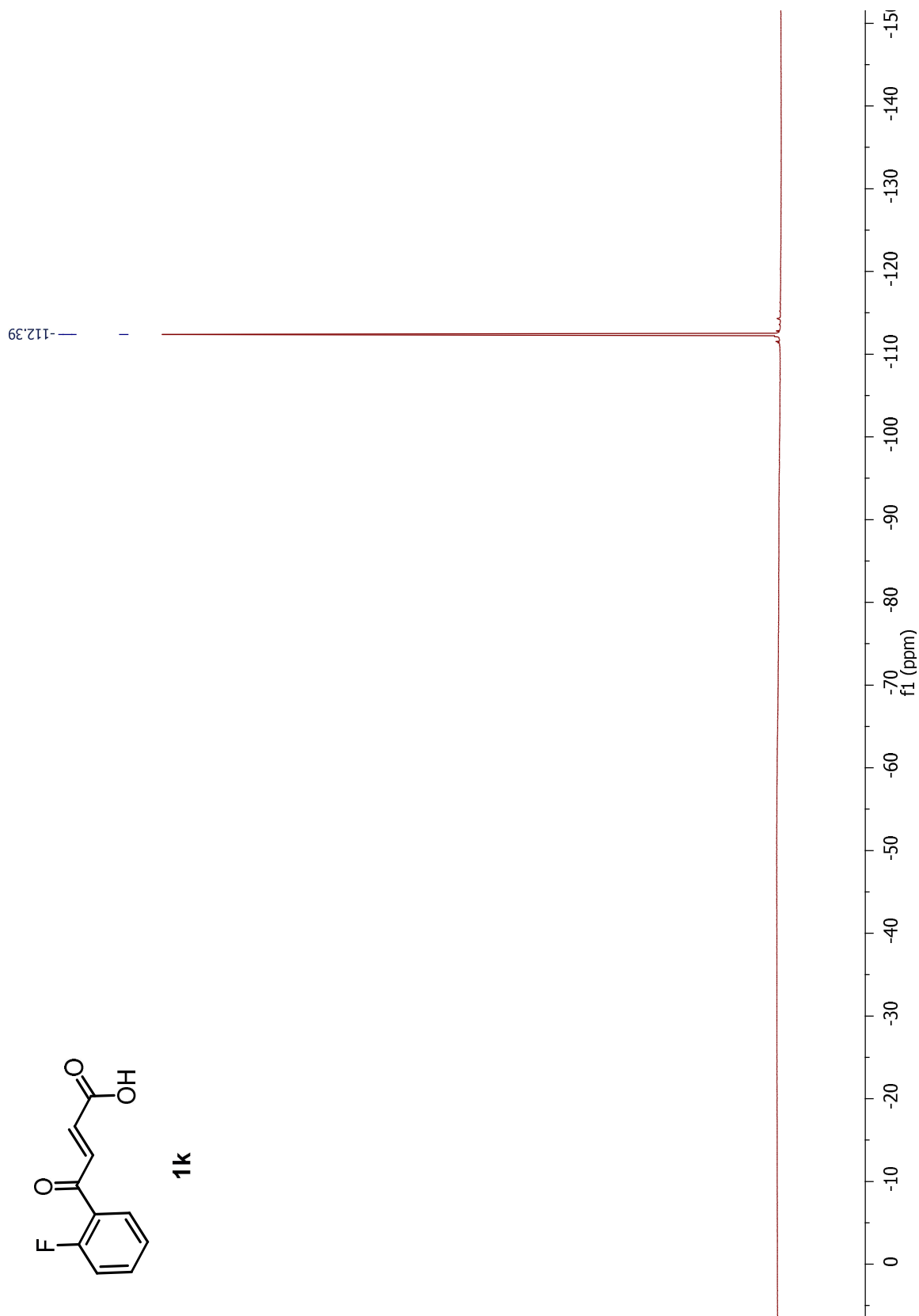


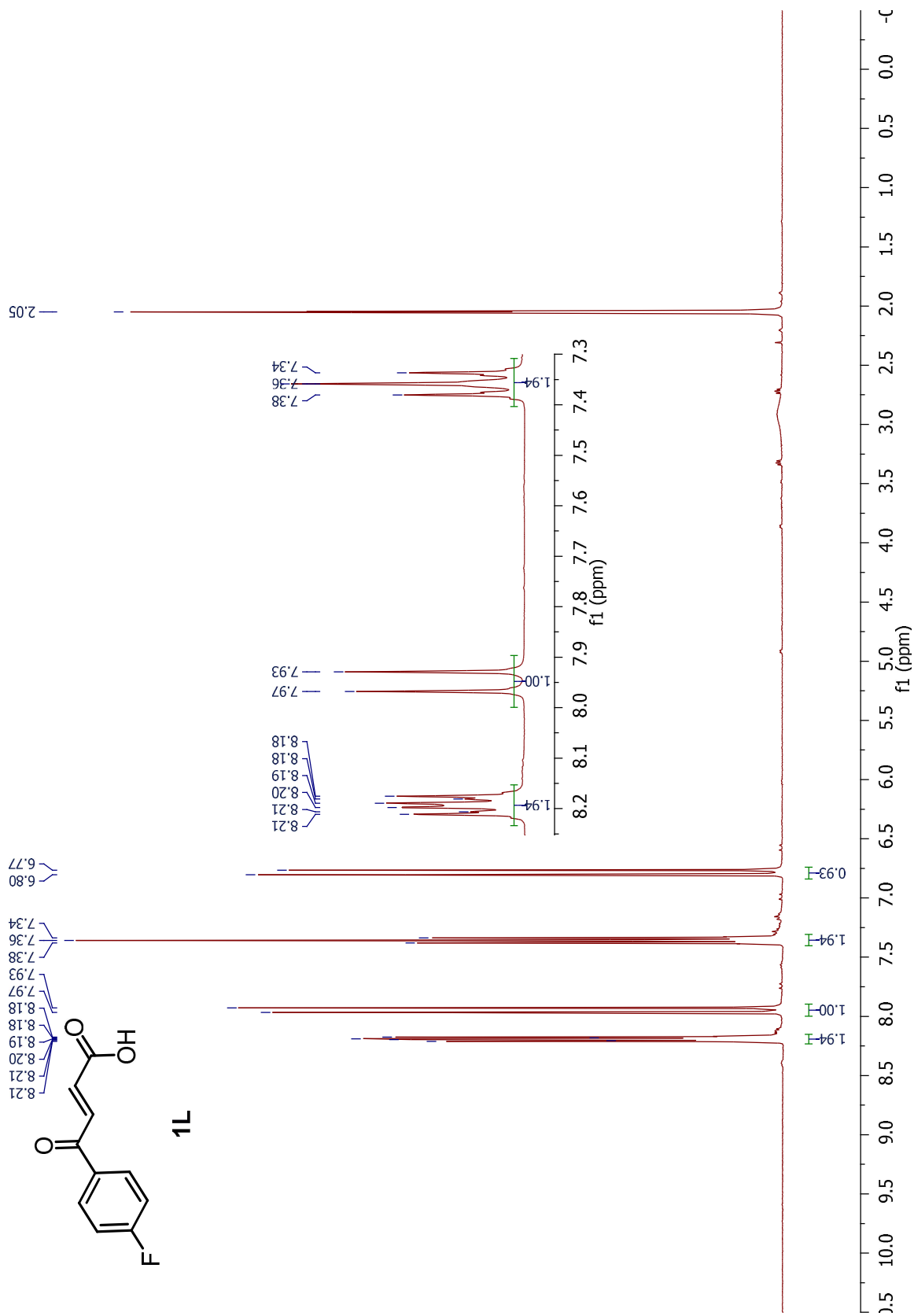


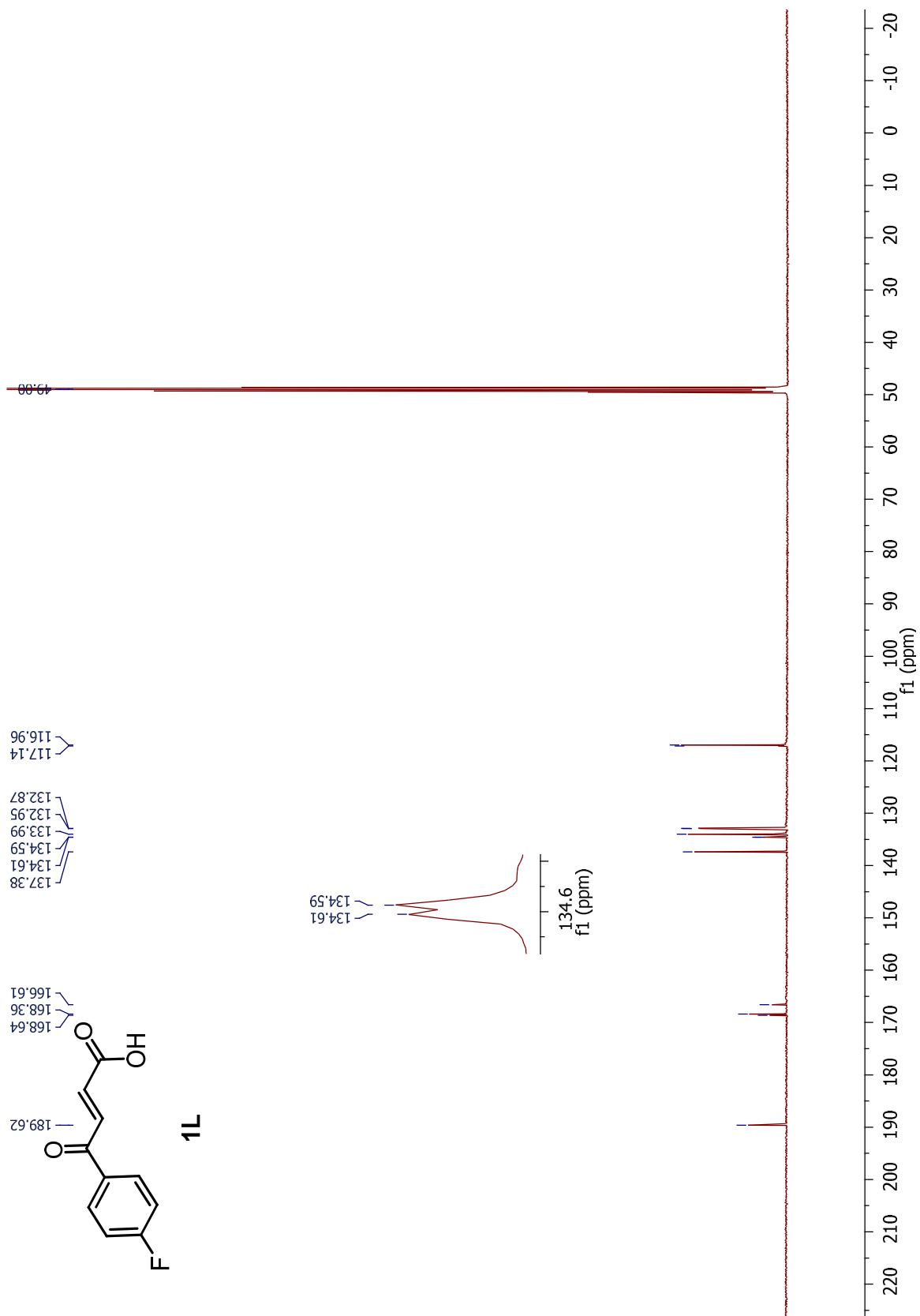


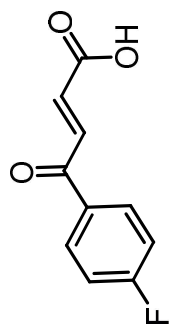


1k

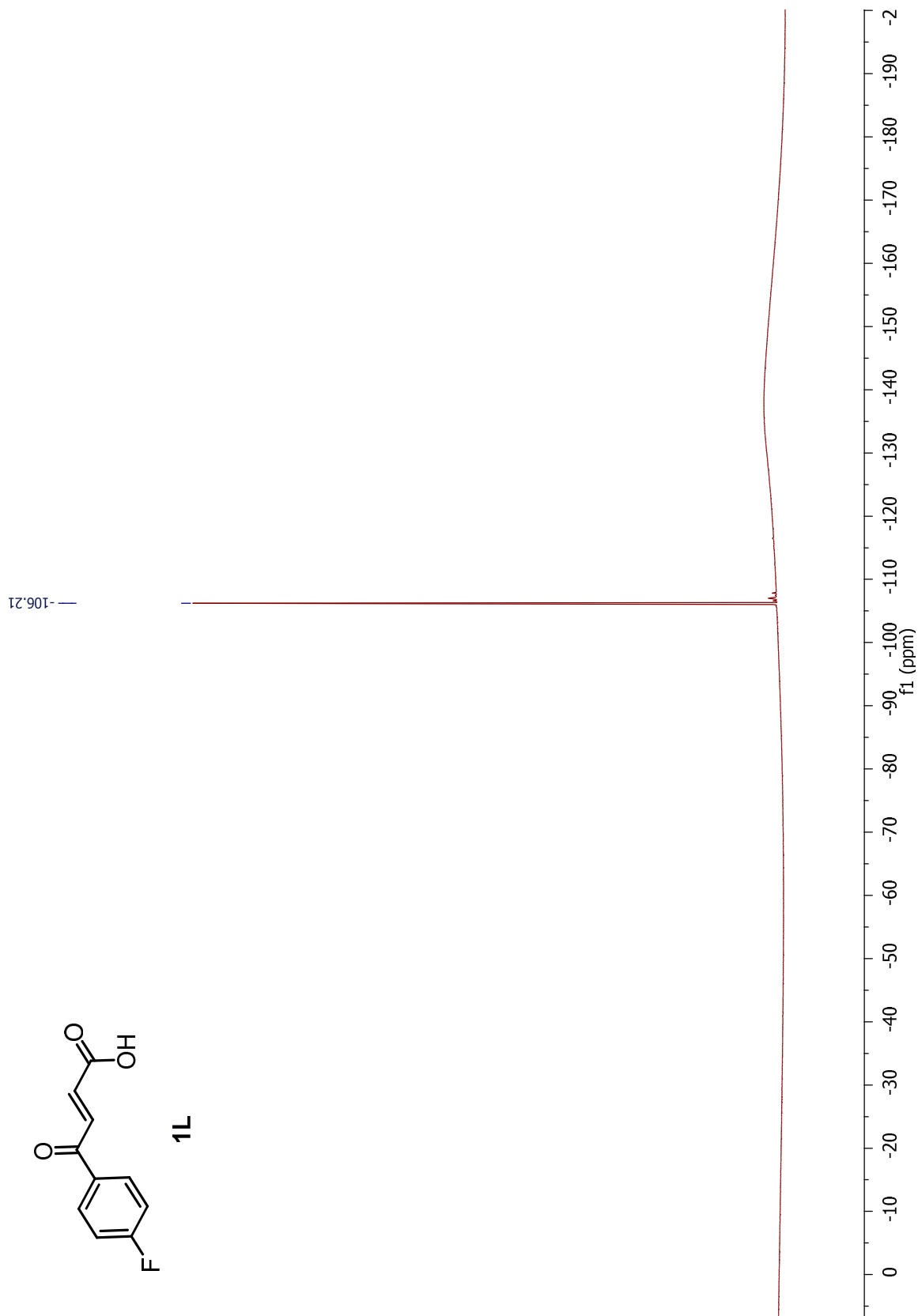


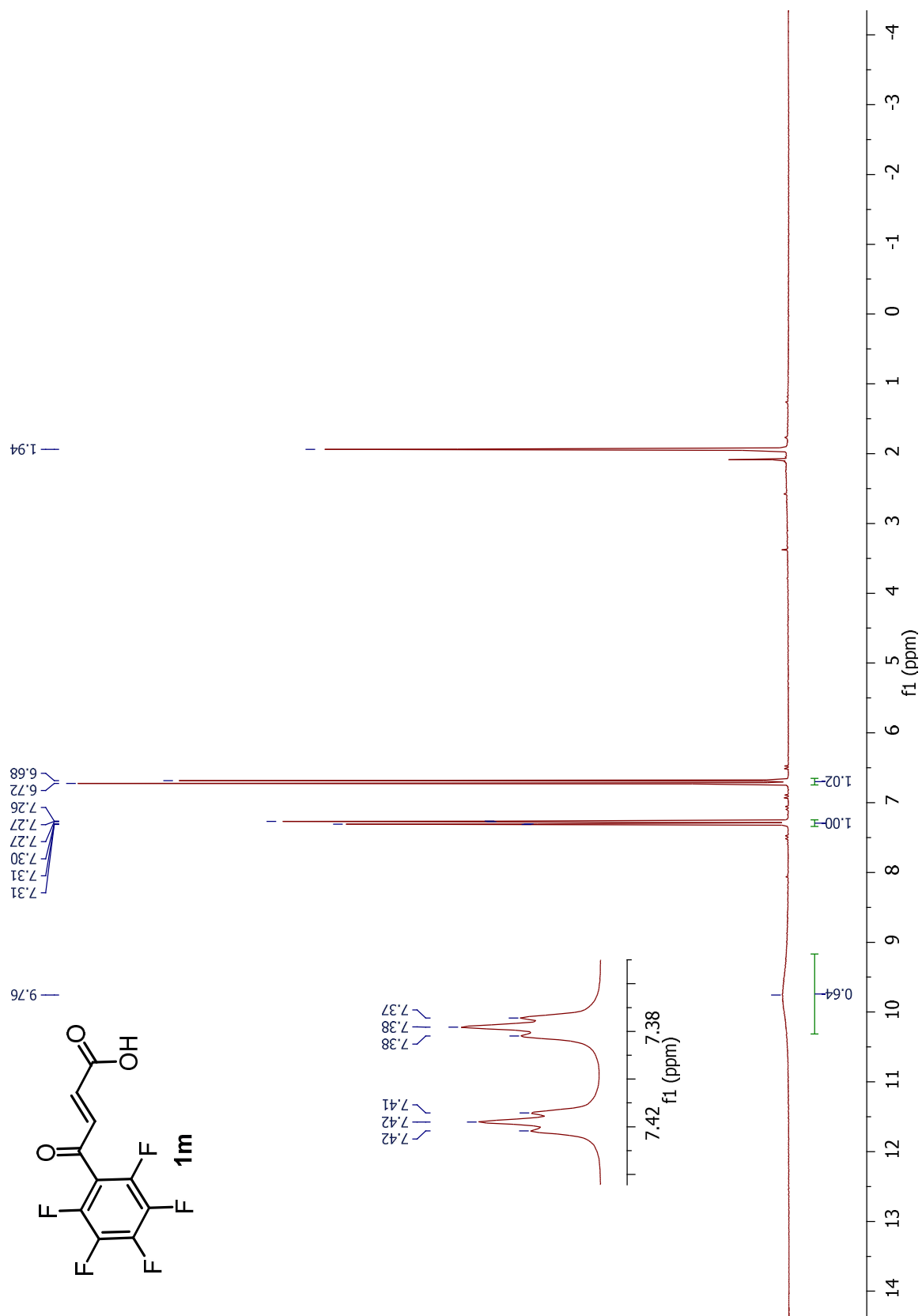


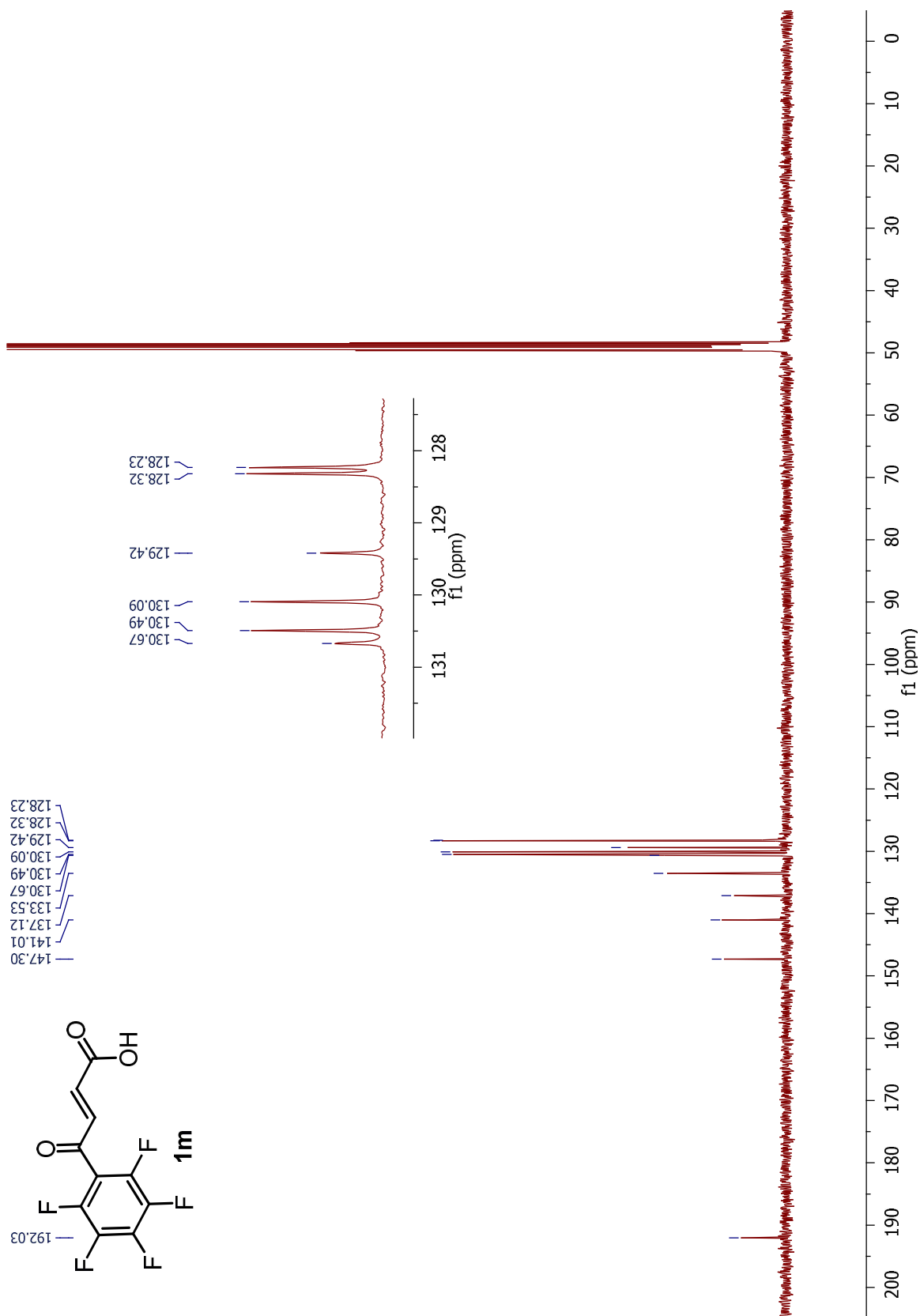


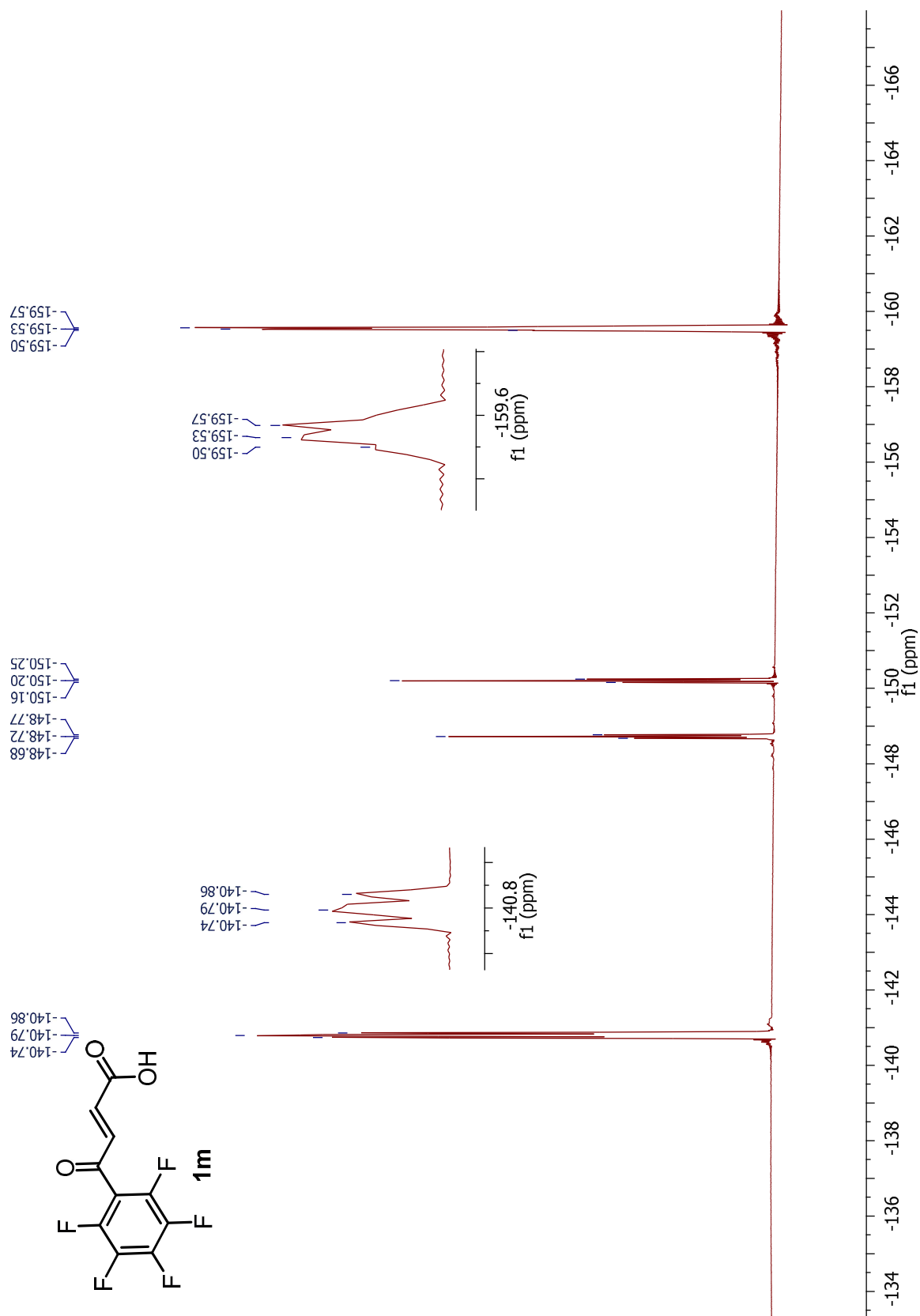


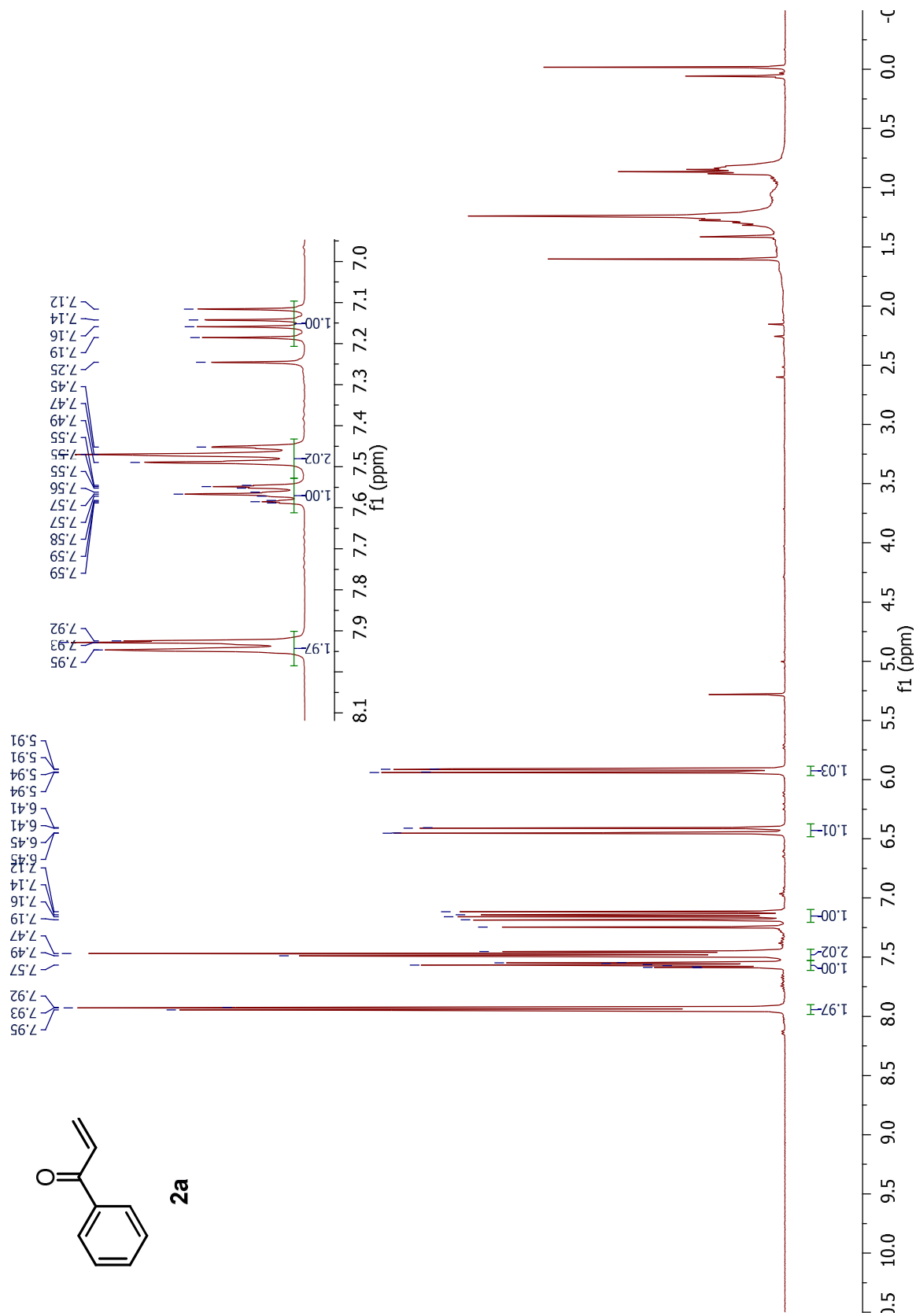
1L

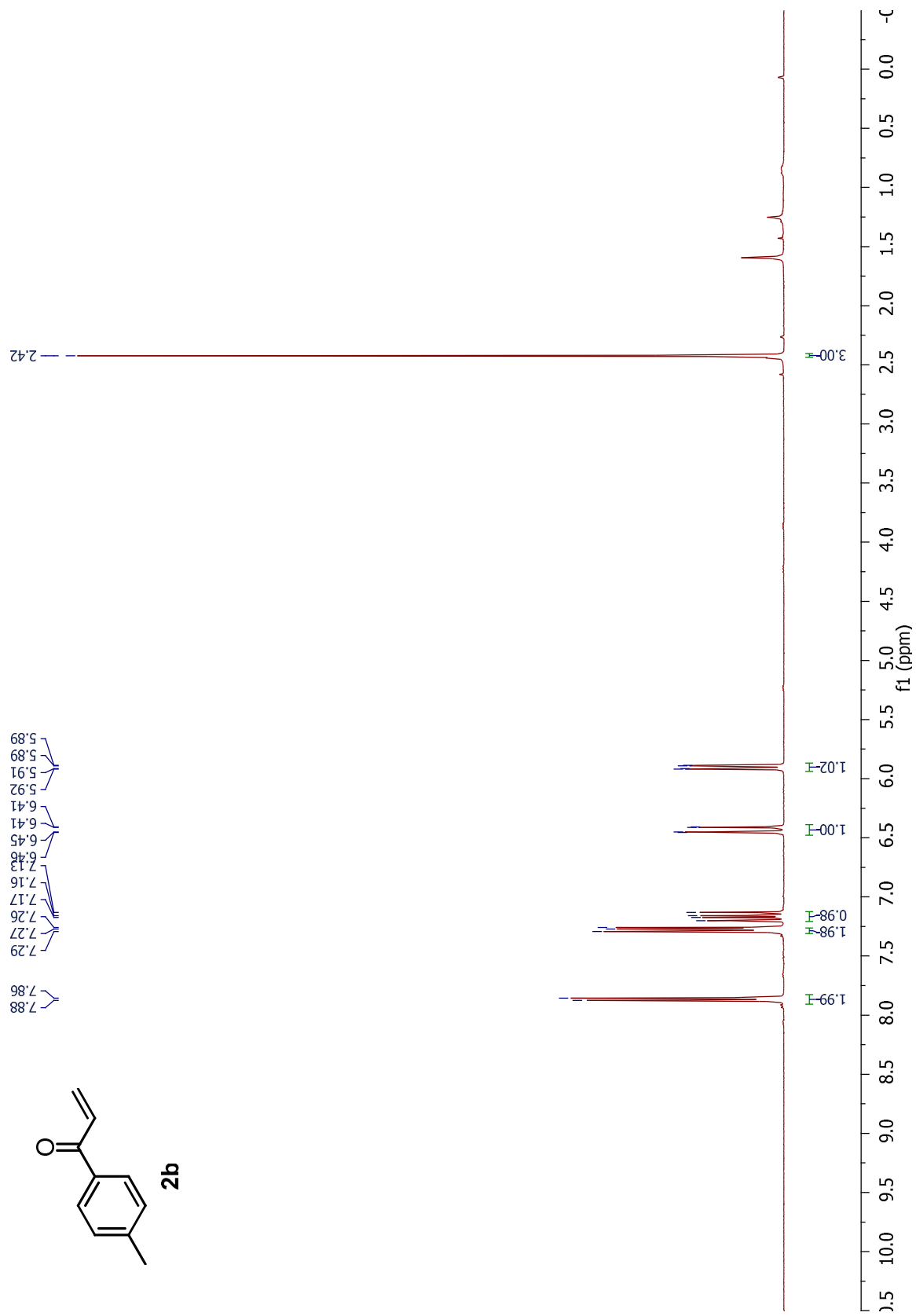


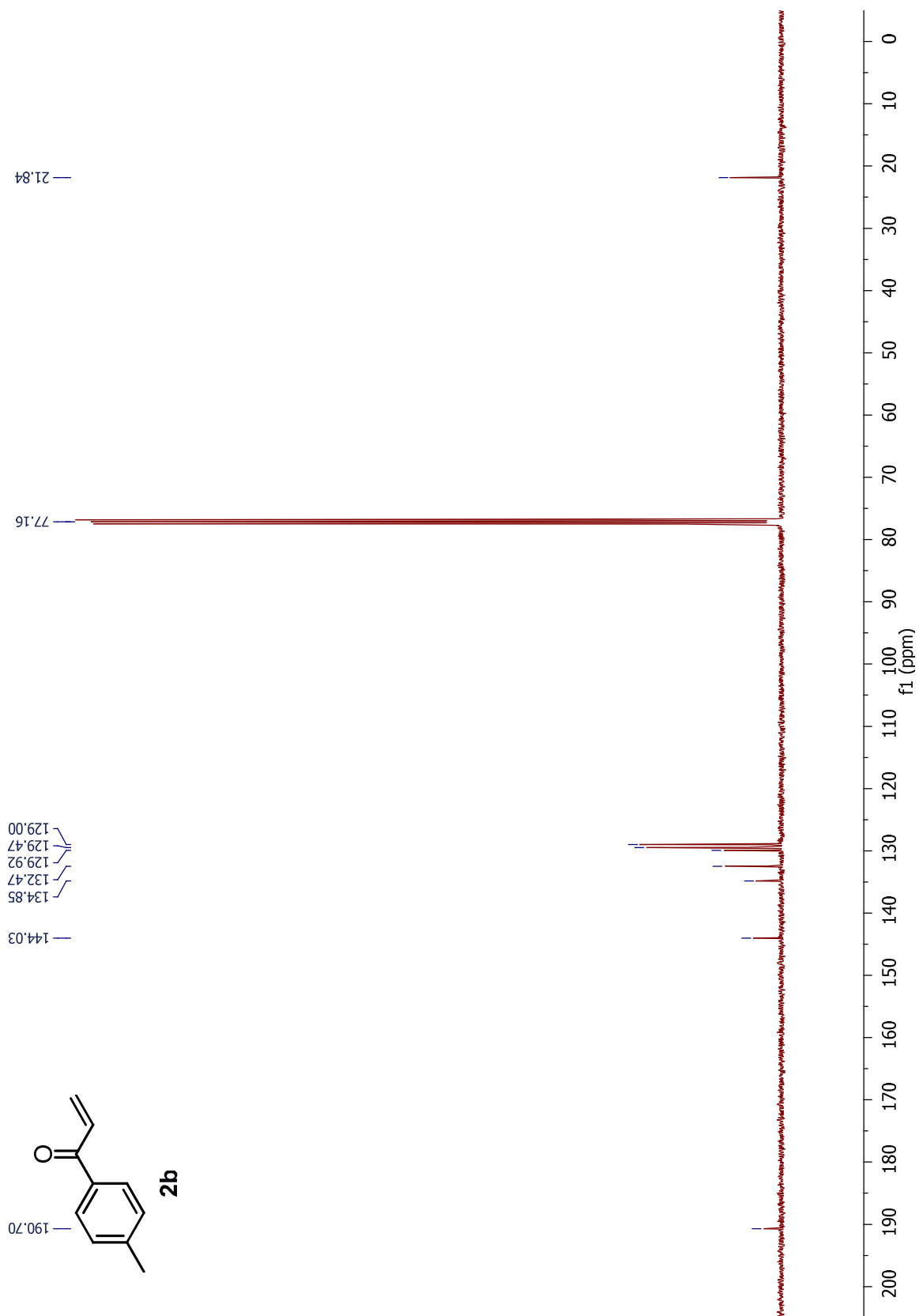


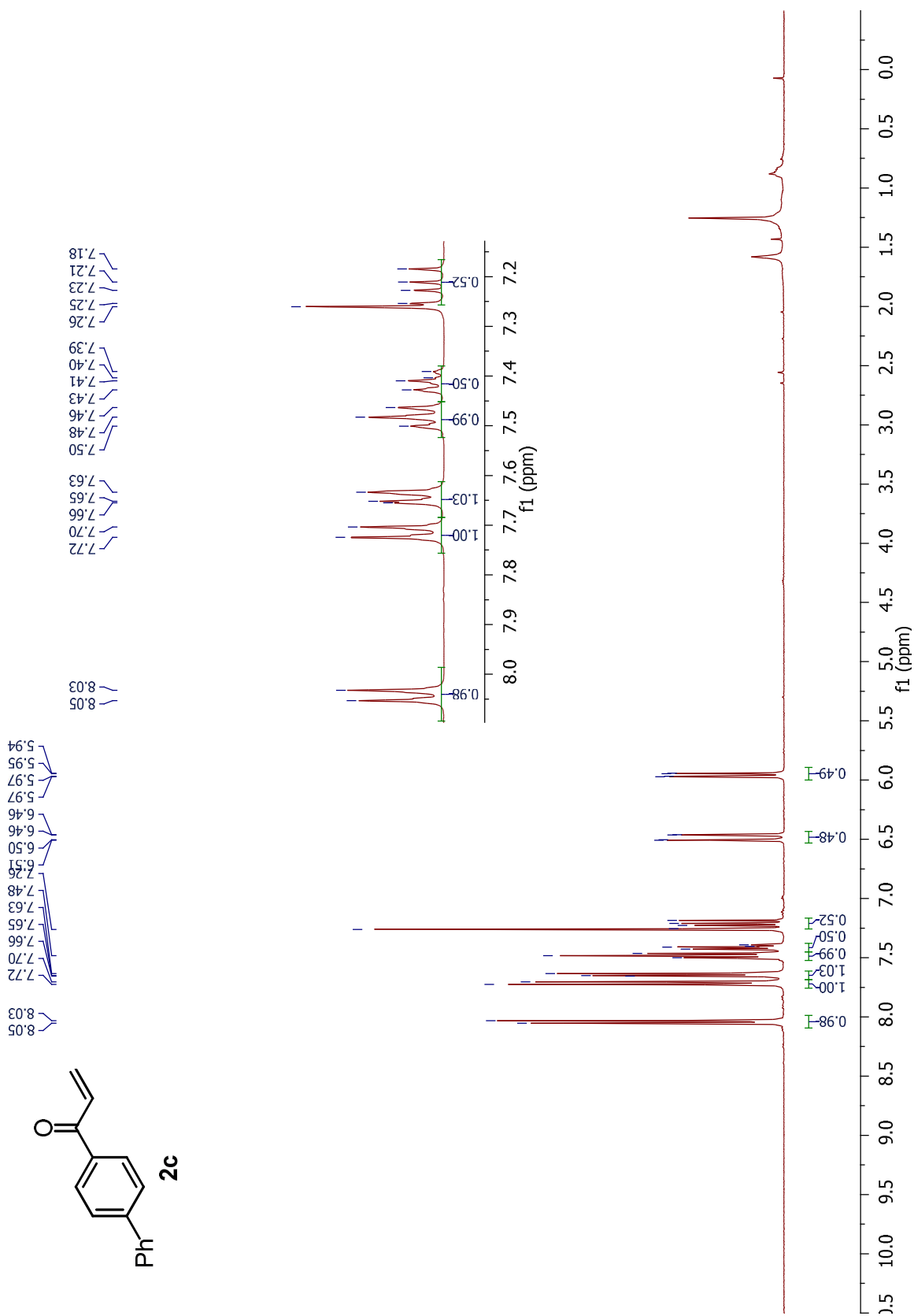


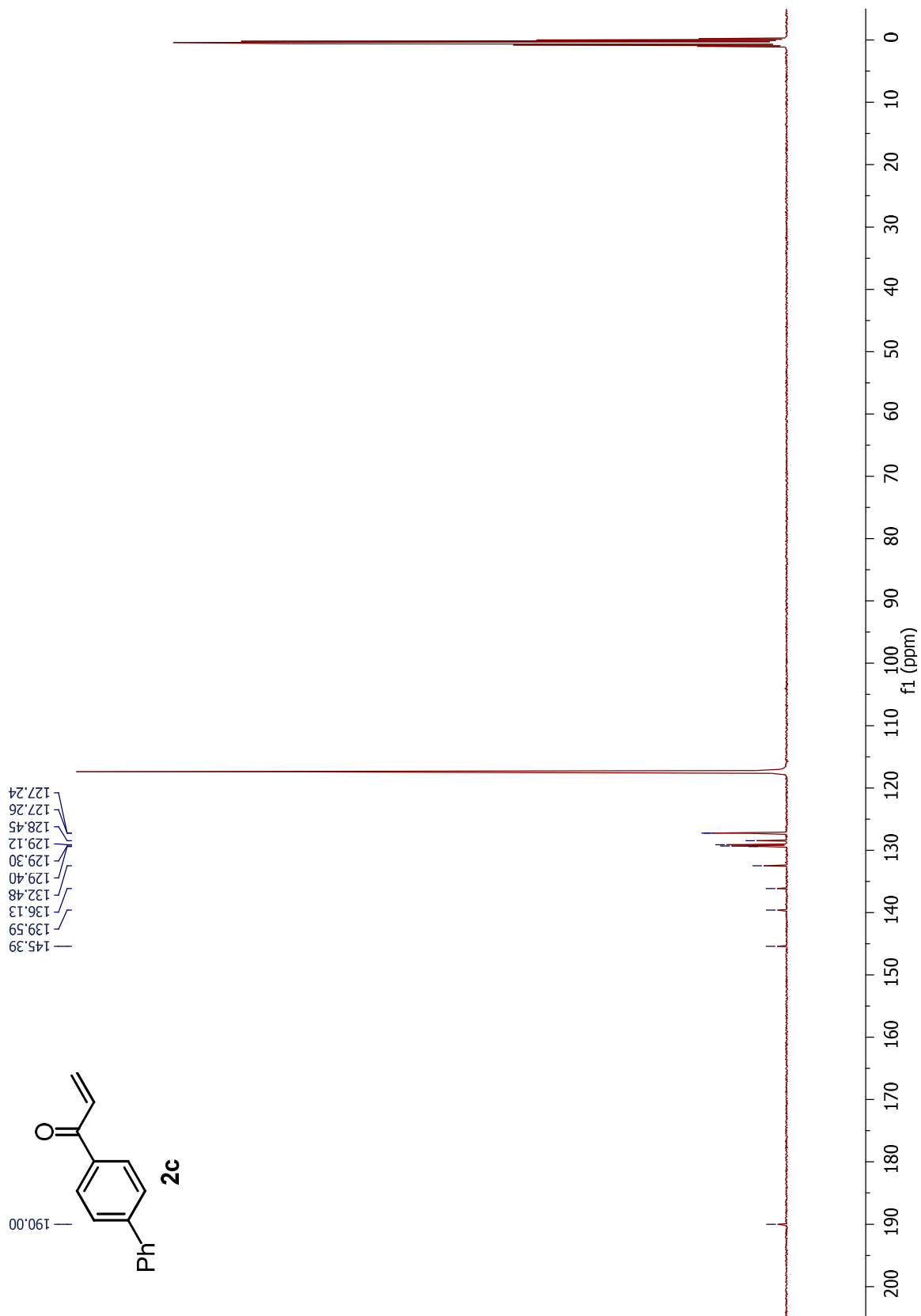


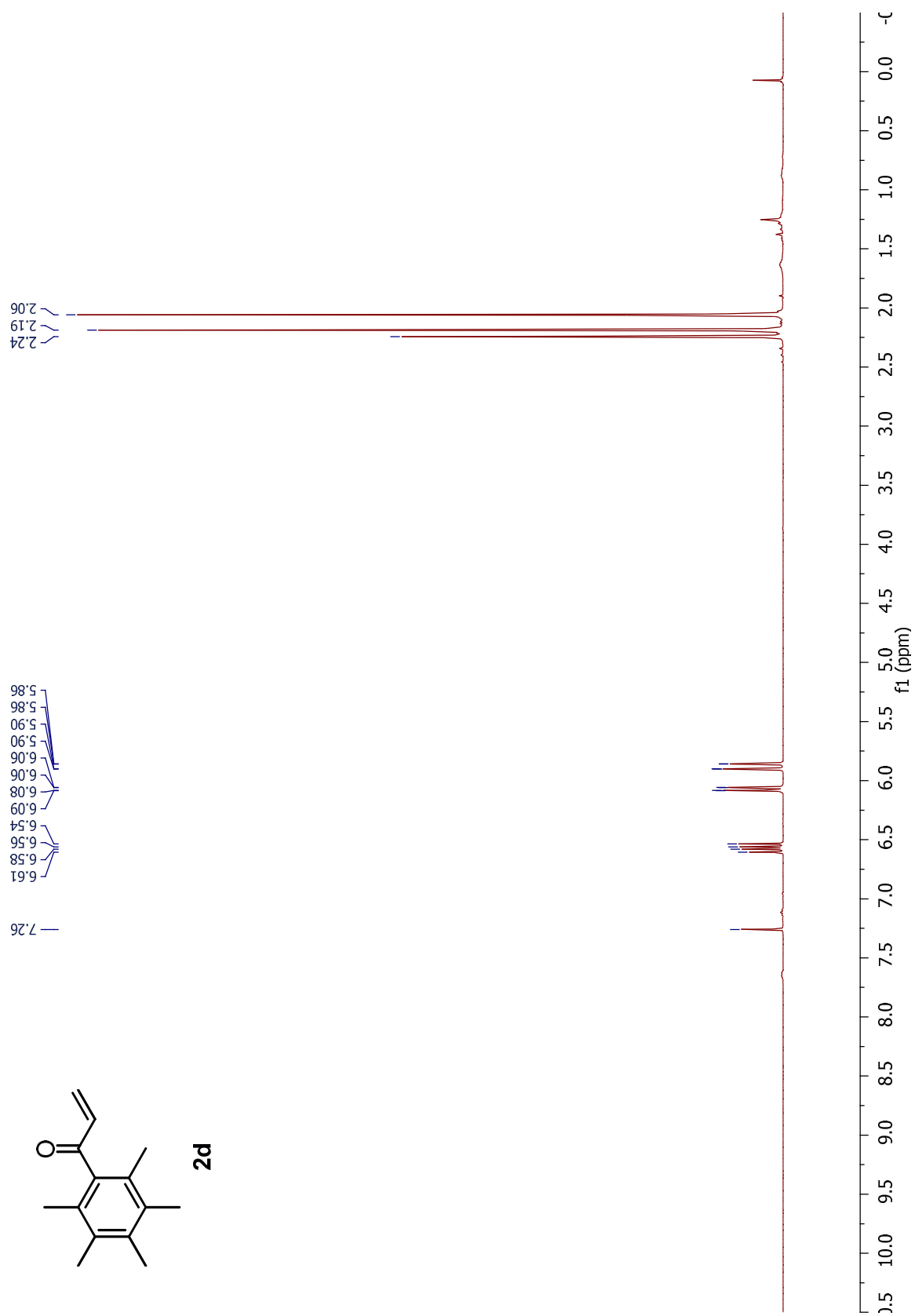


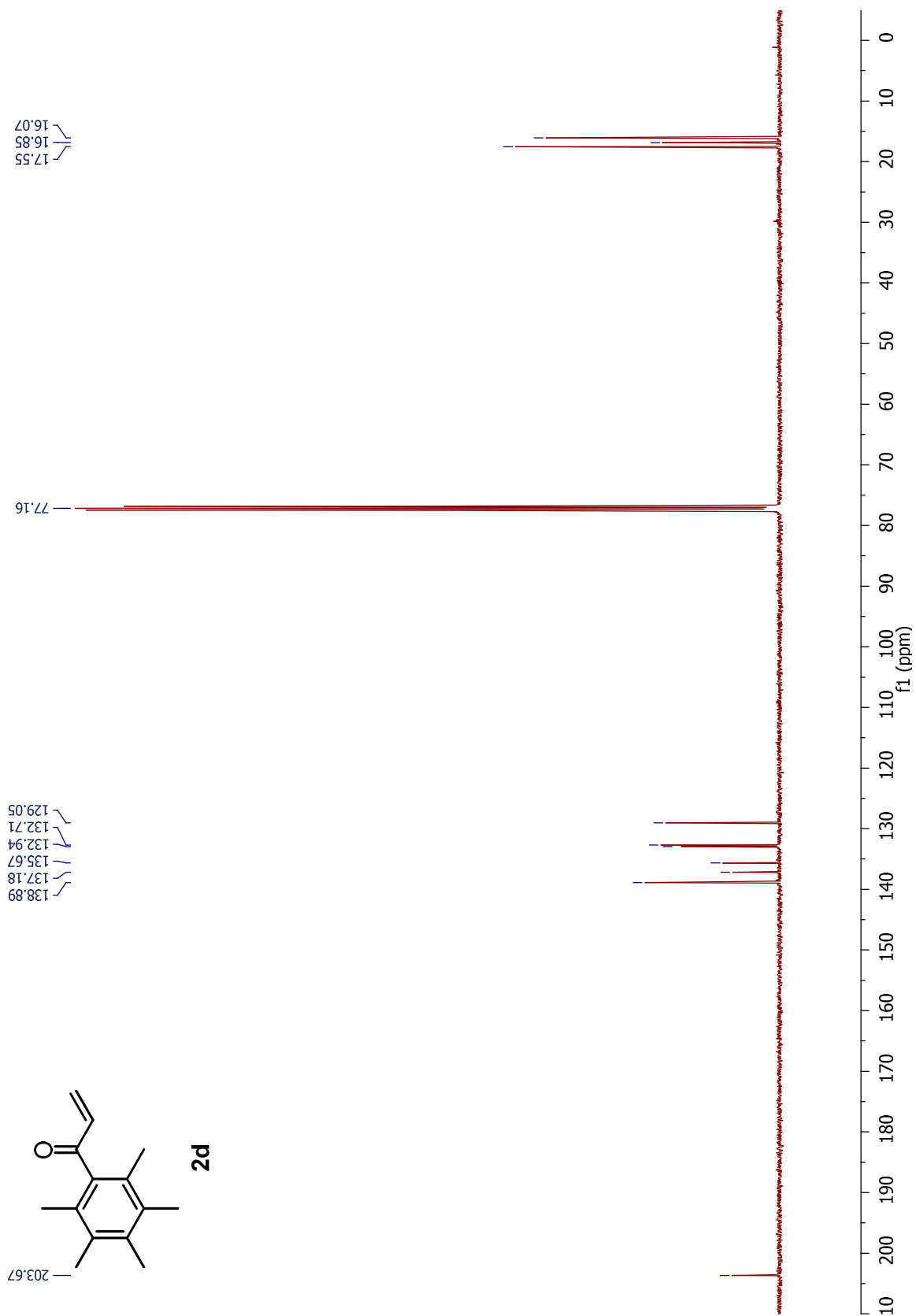


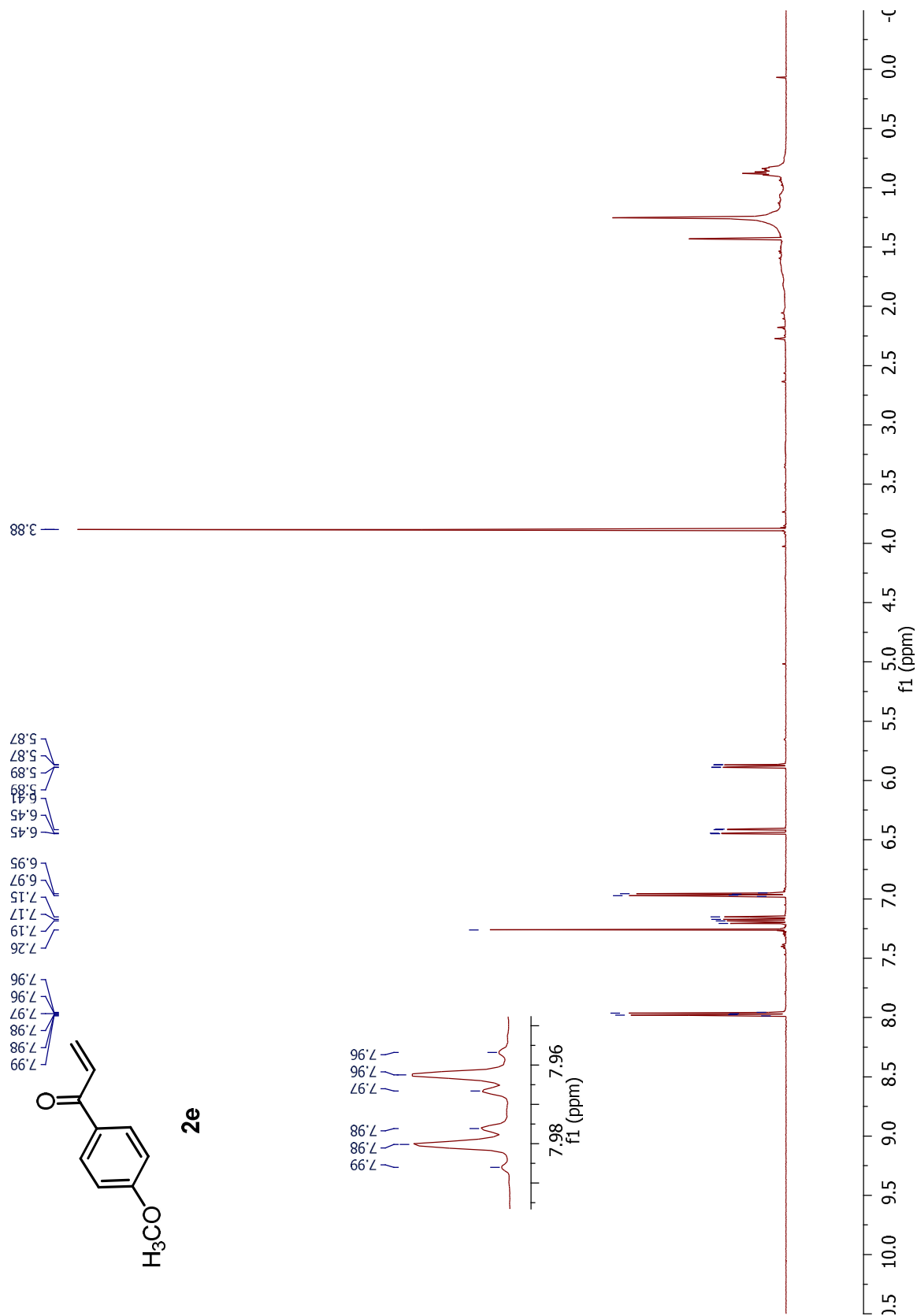


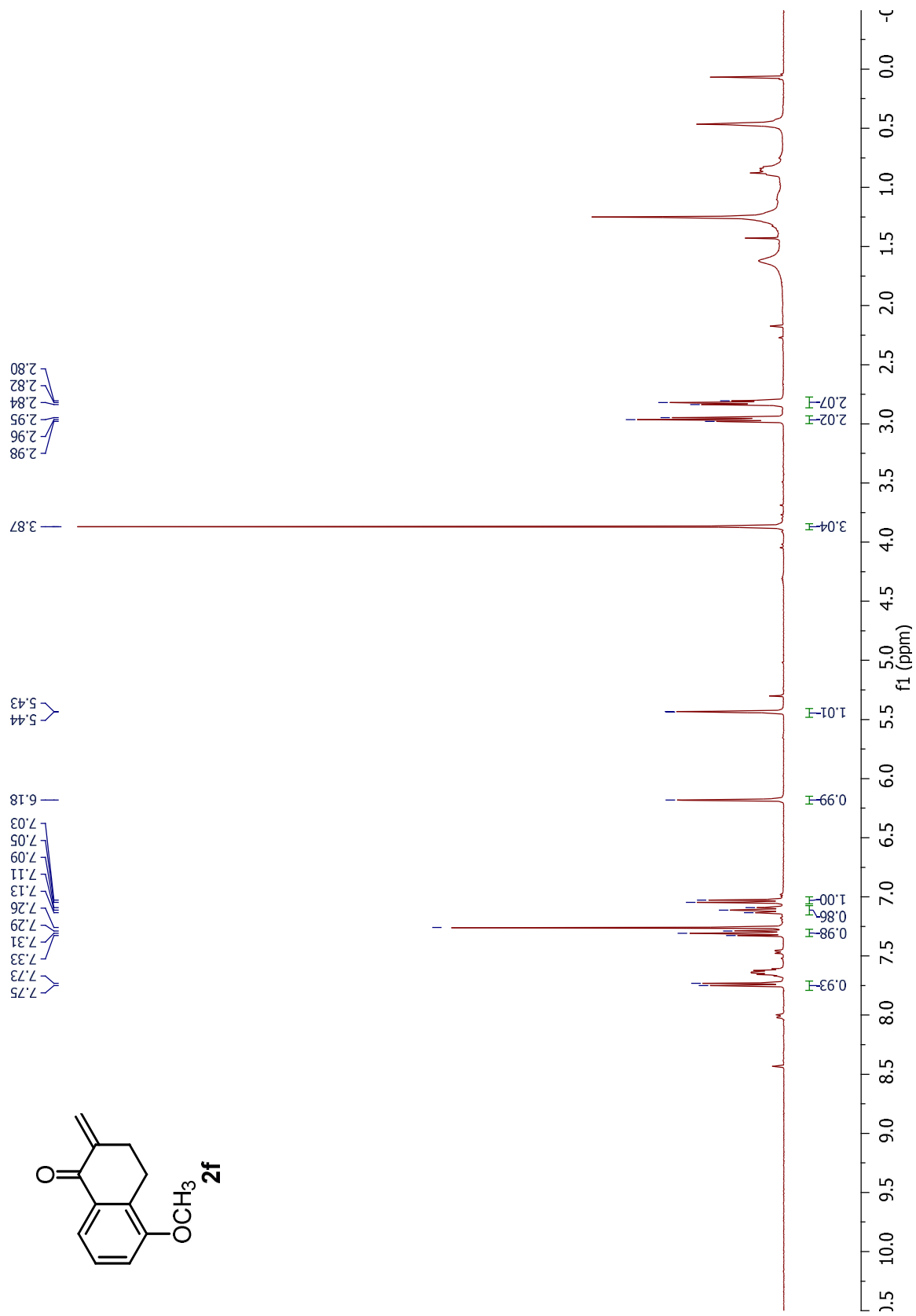


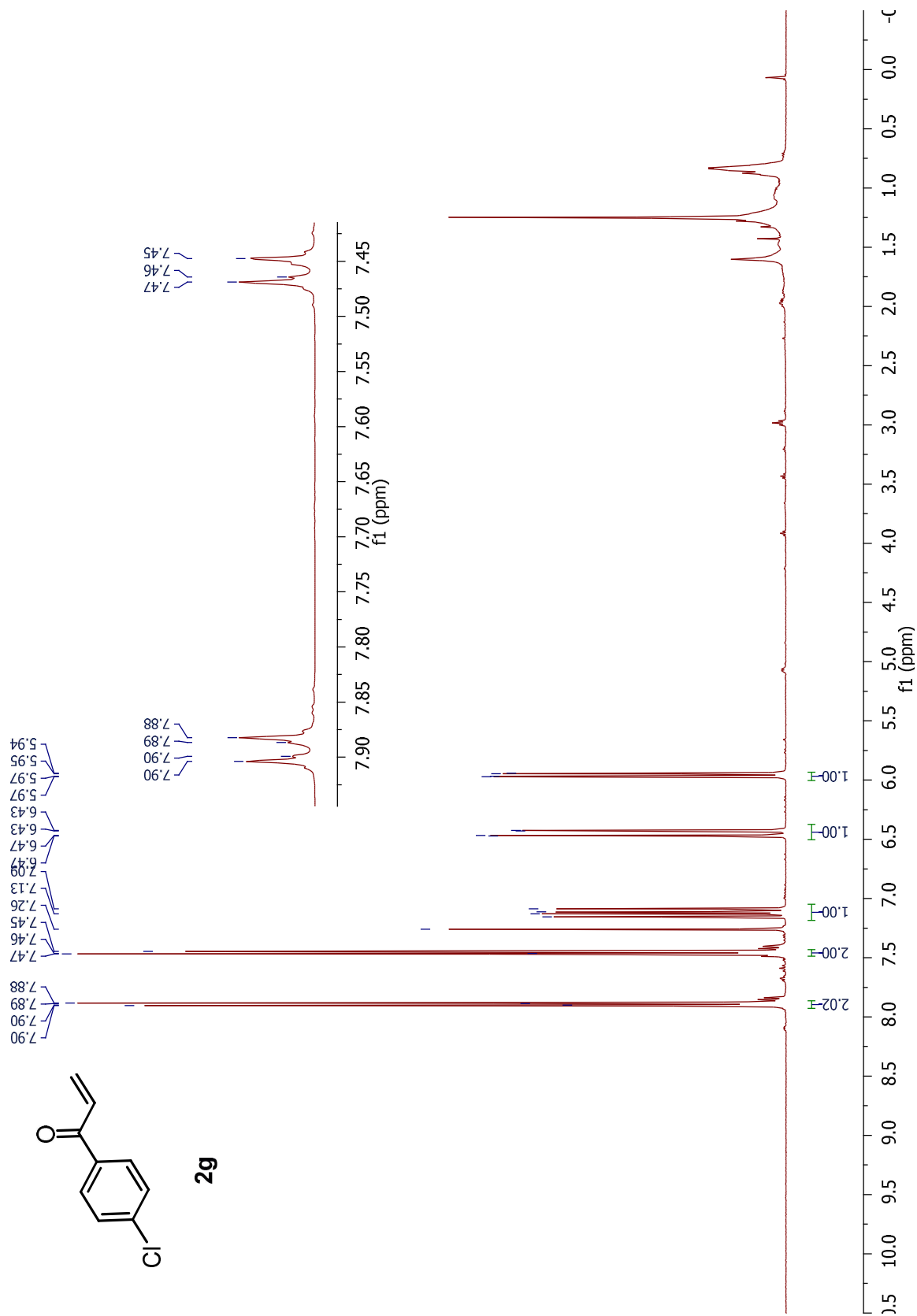


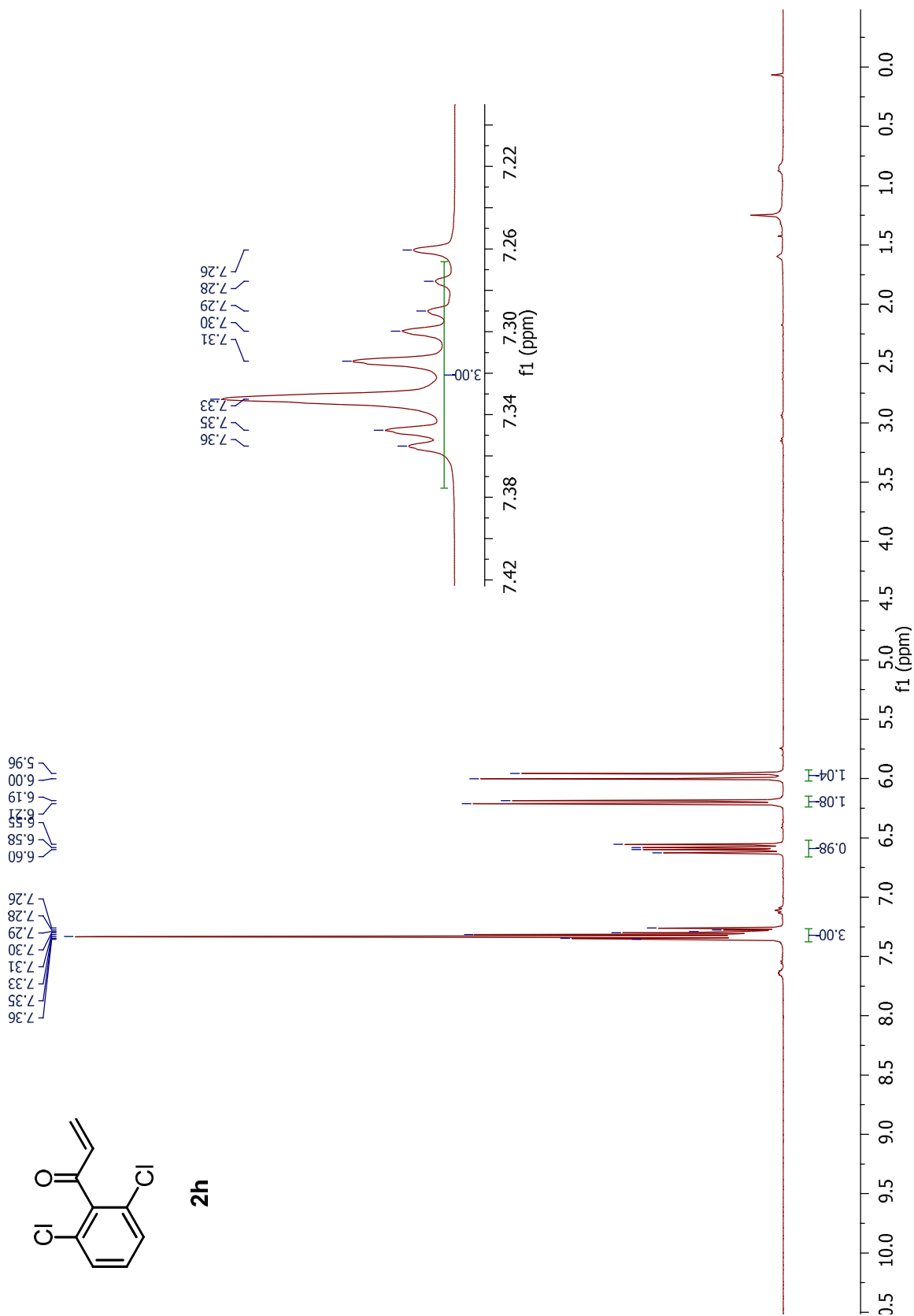


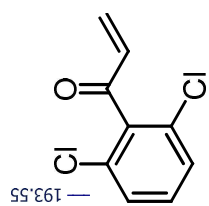






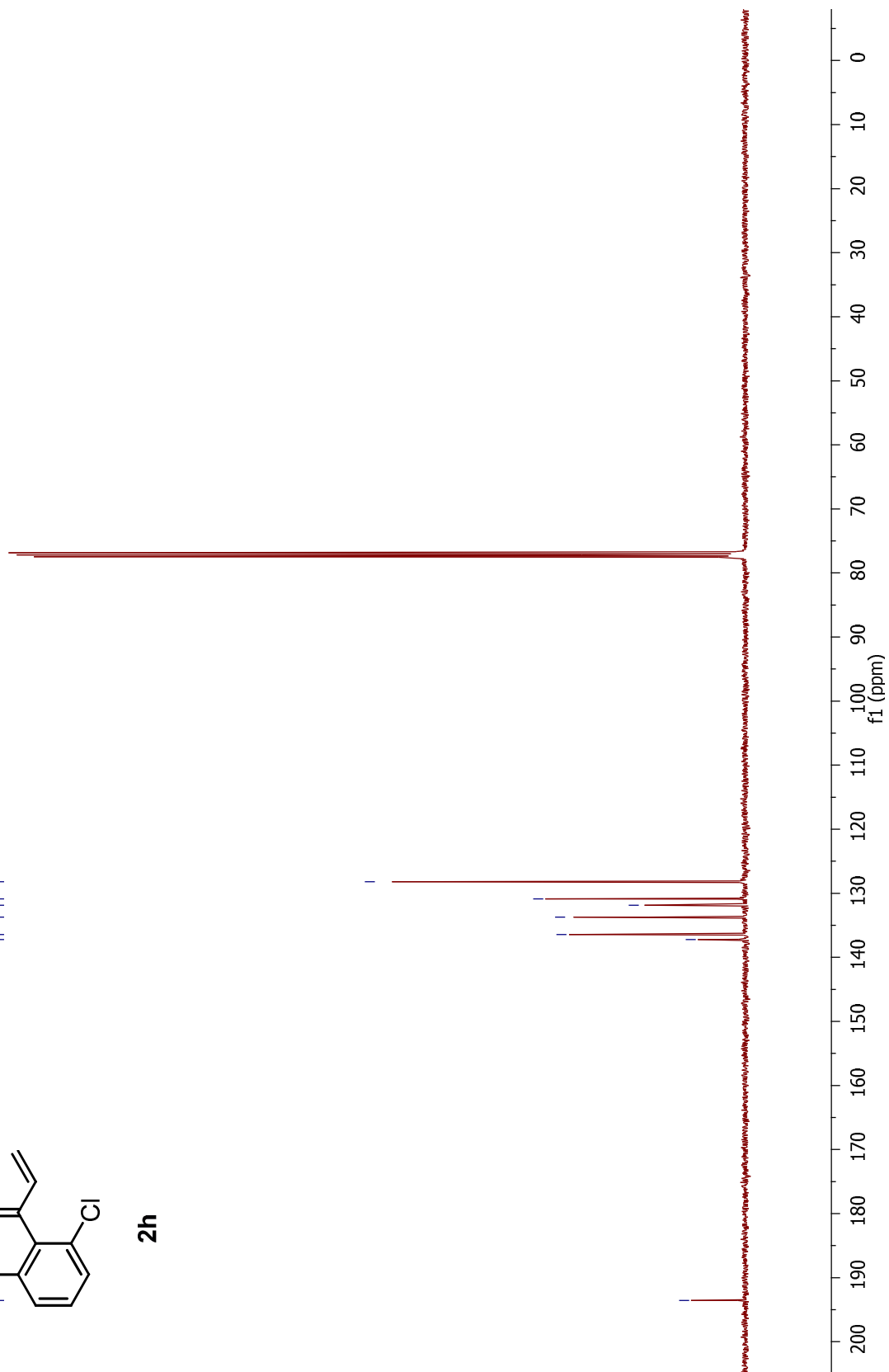


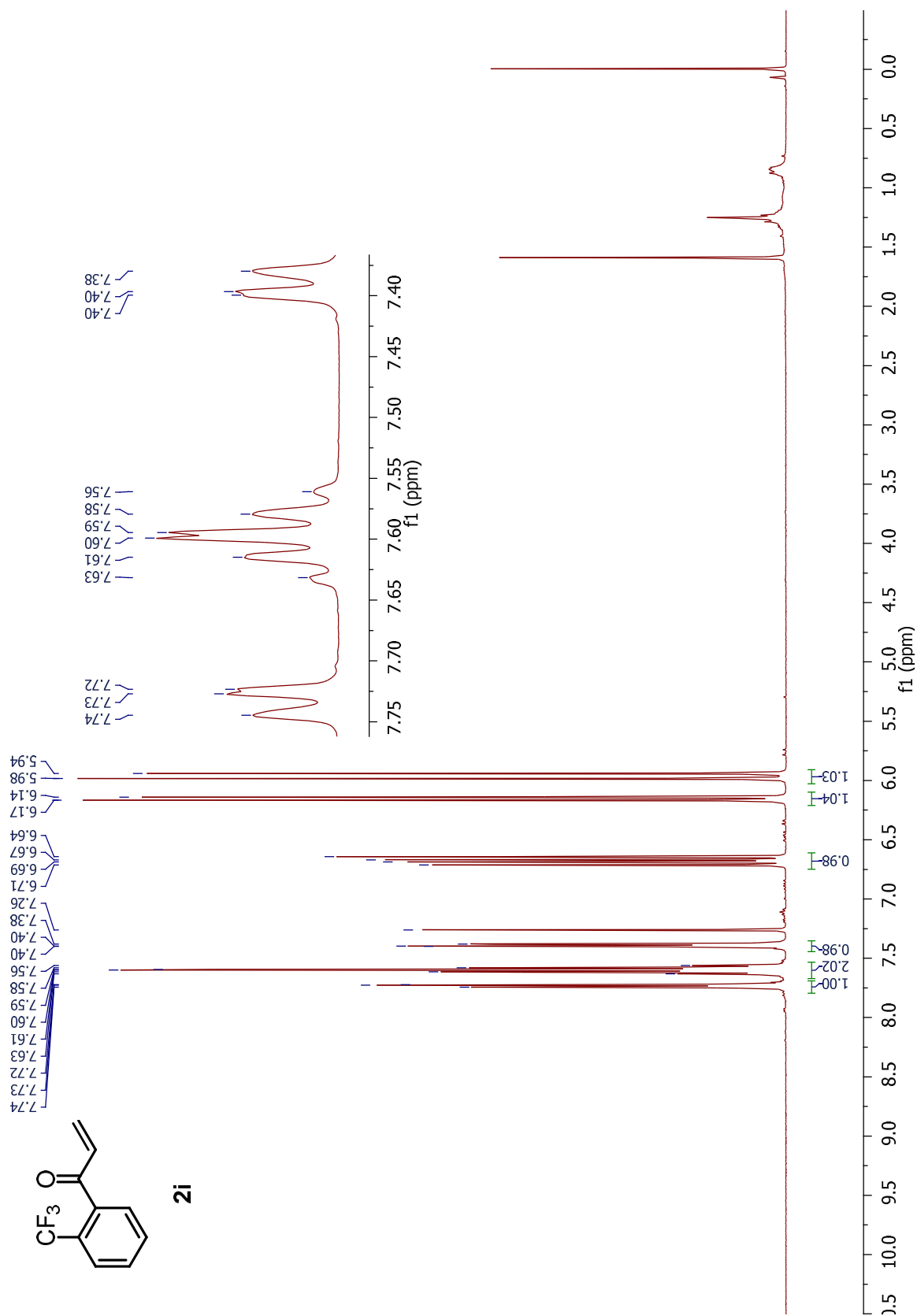


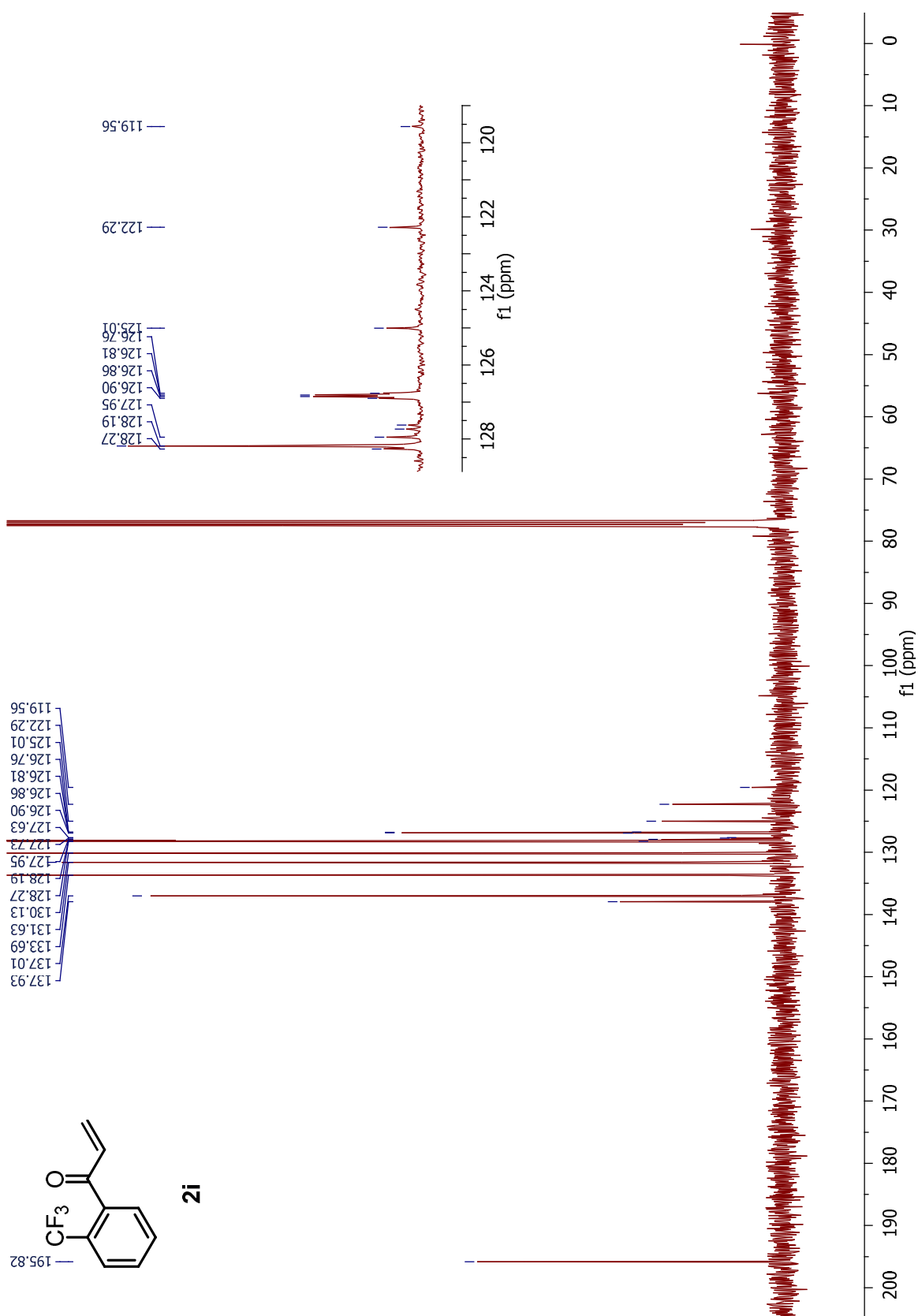


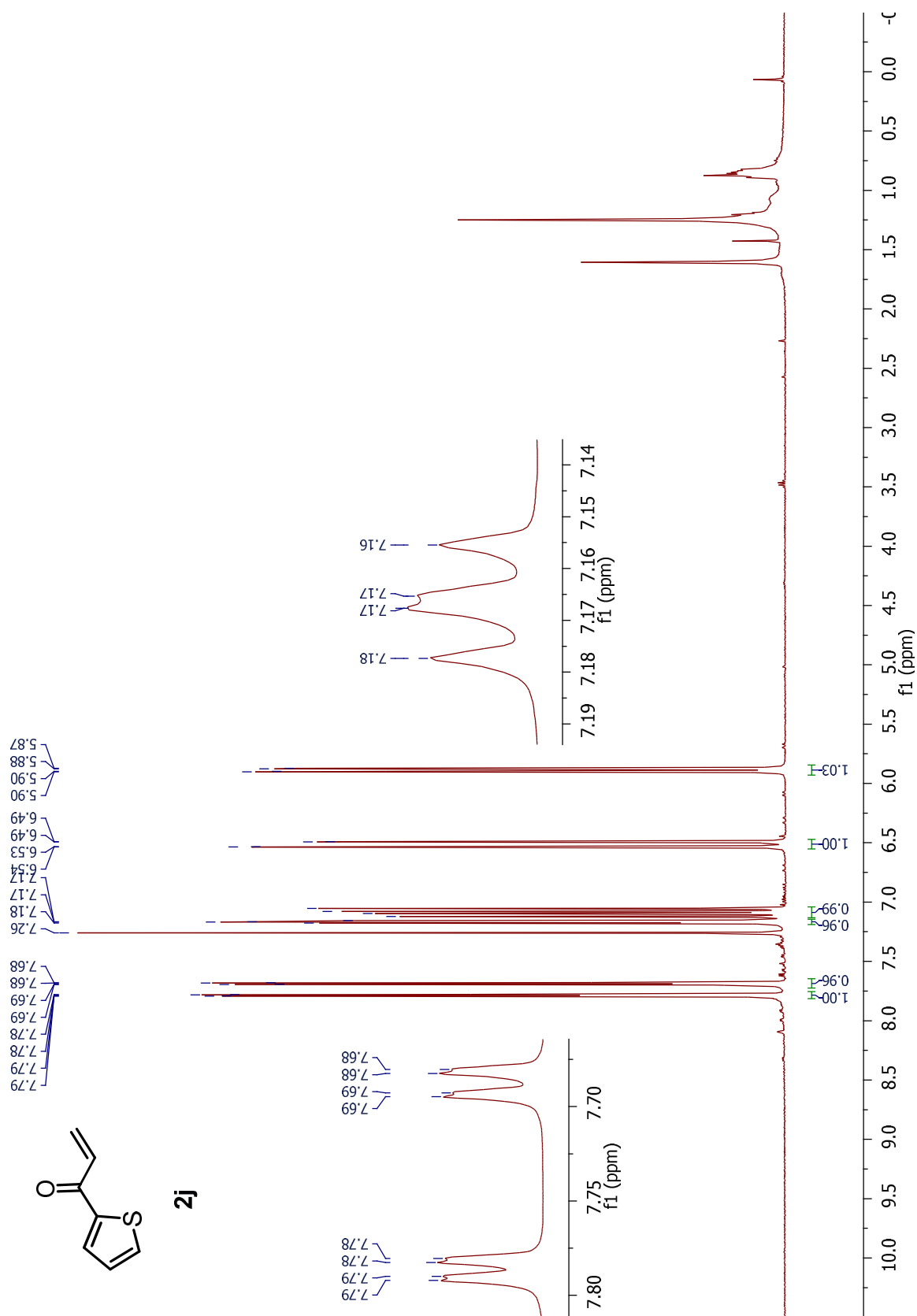
2h

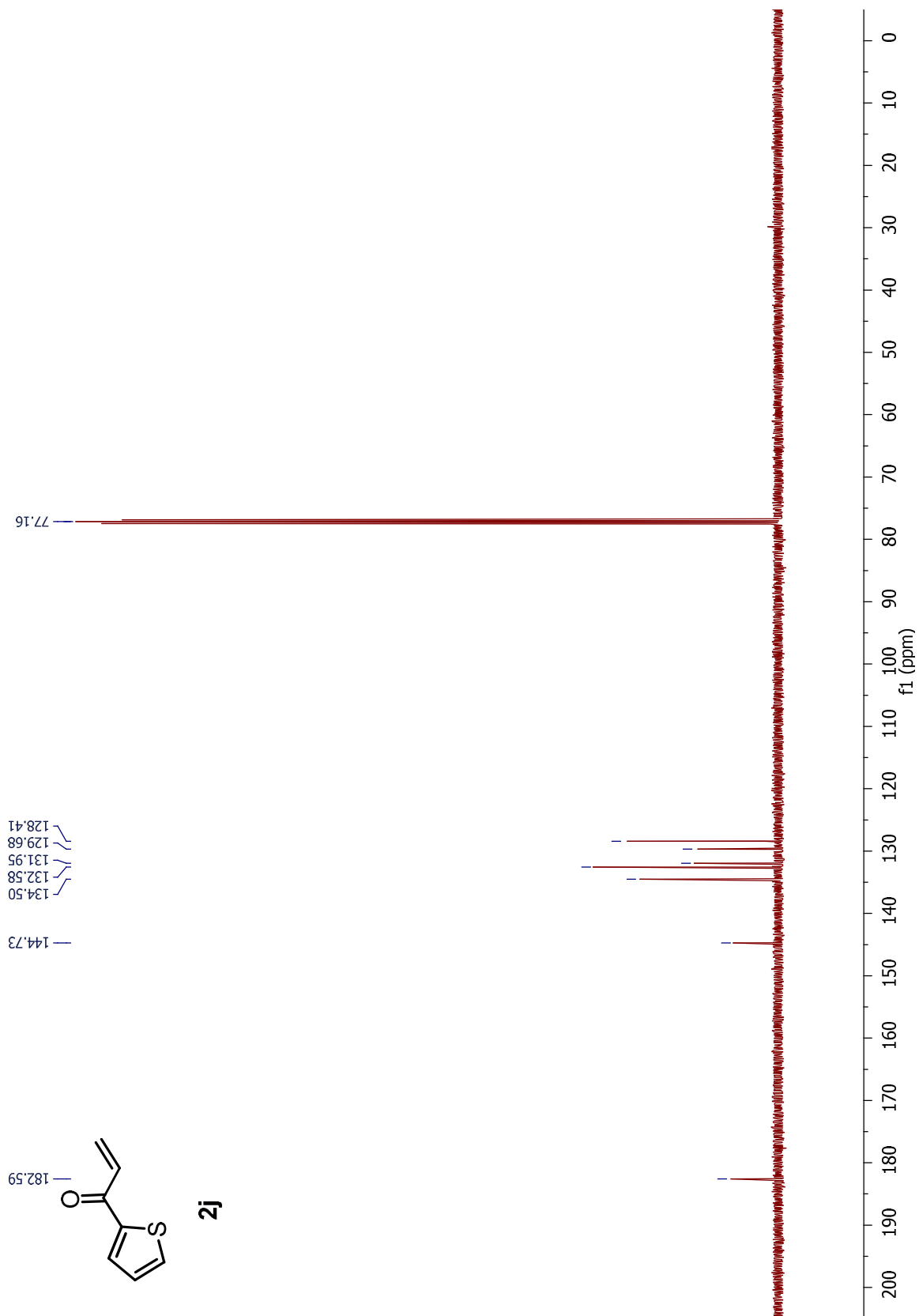
193.55
137.21
136.44
133.73
131.86
130.86
128.21

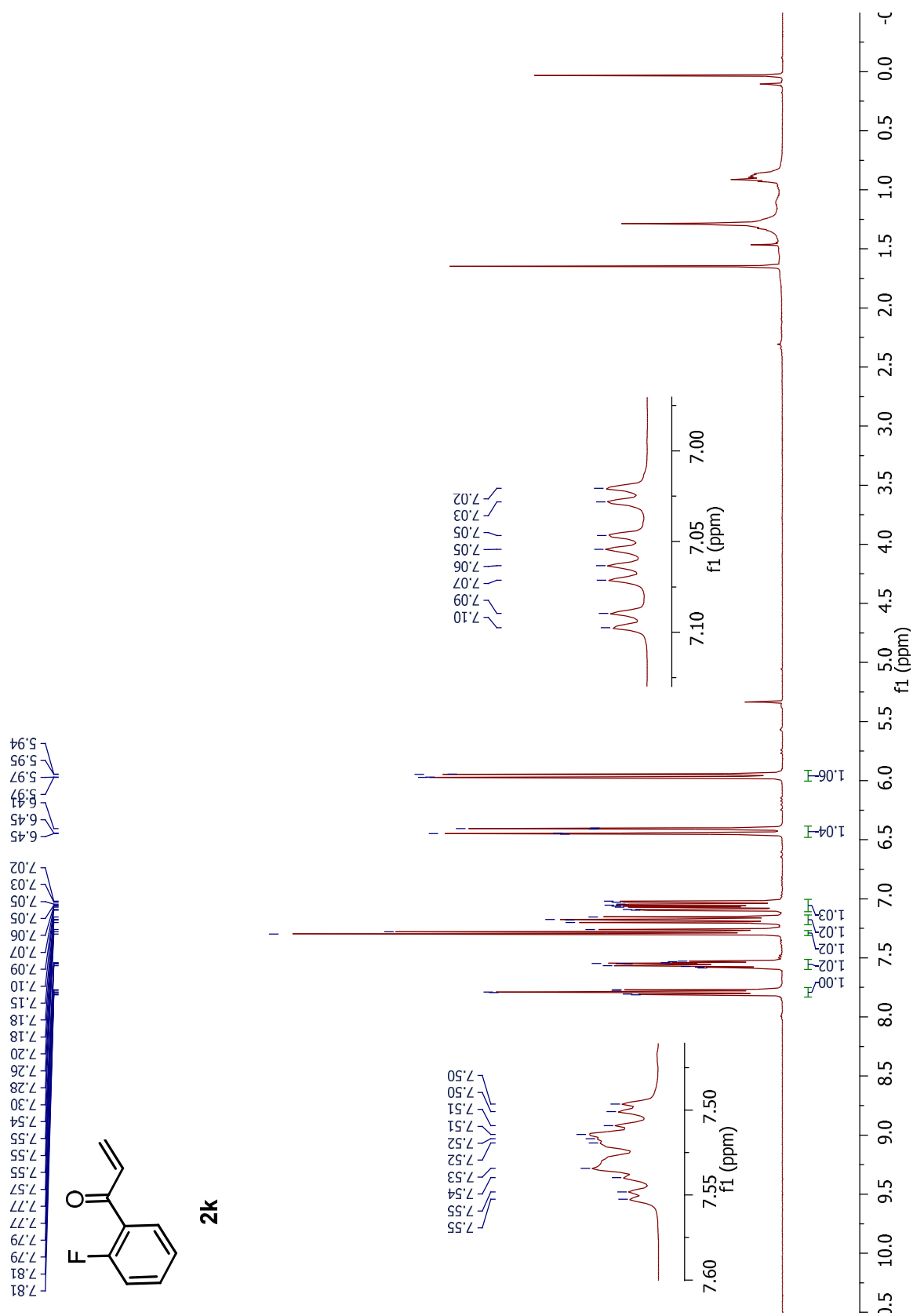


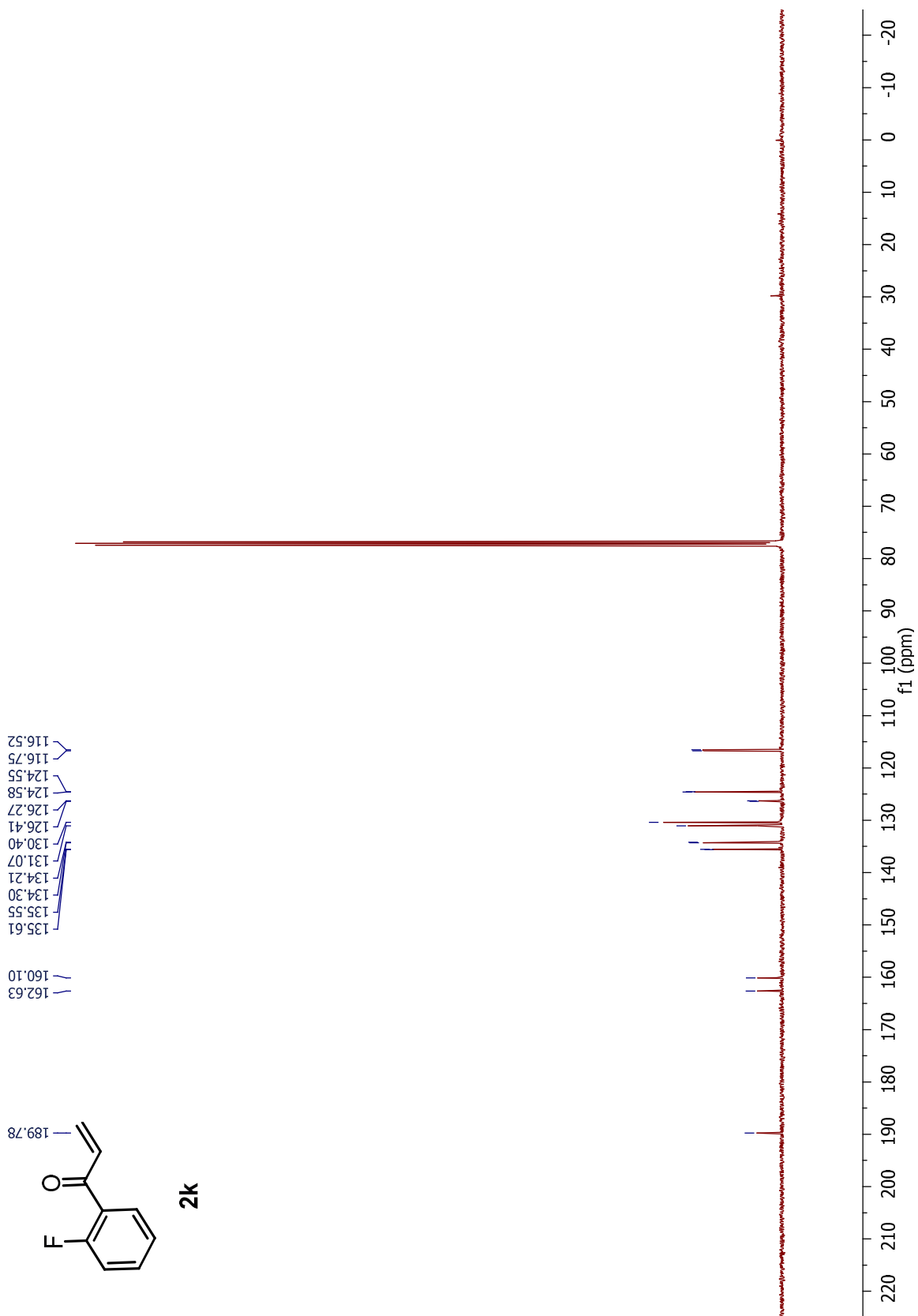


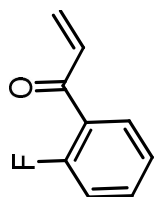




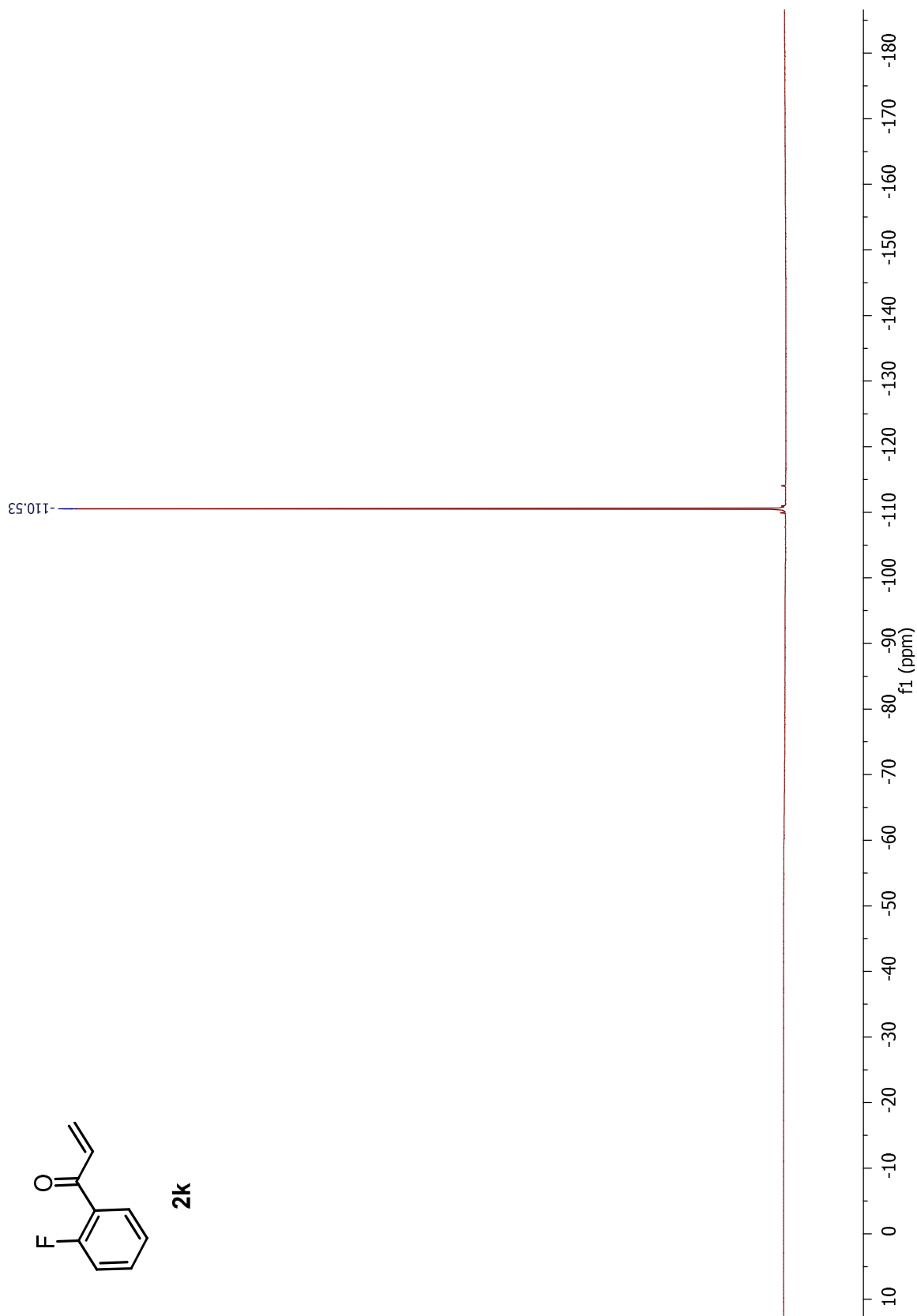


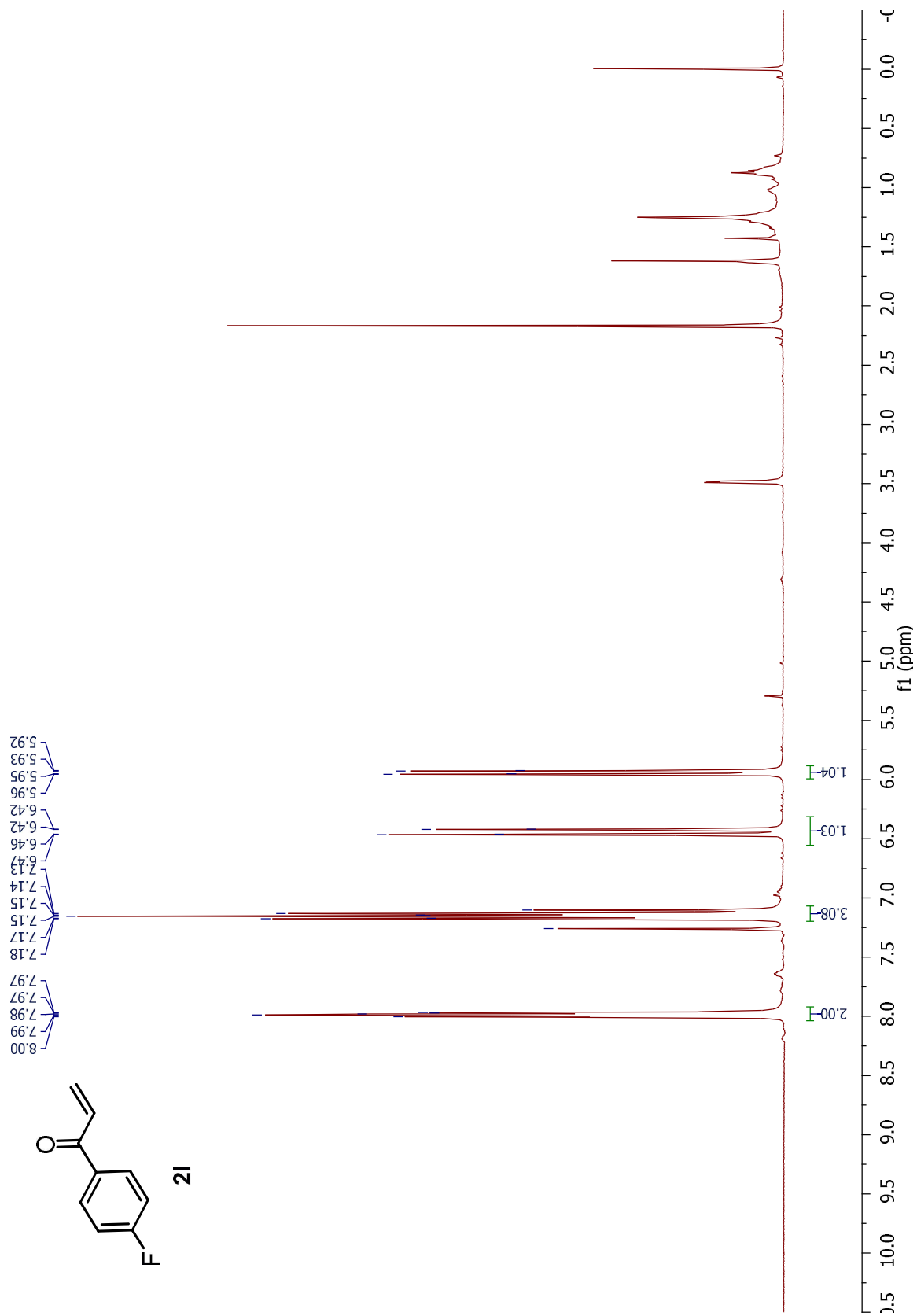


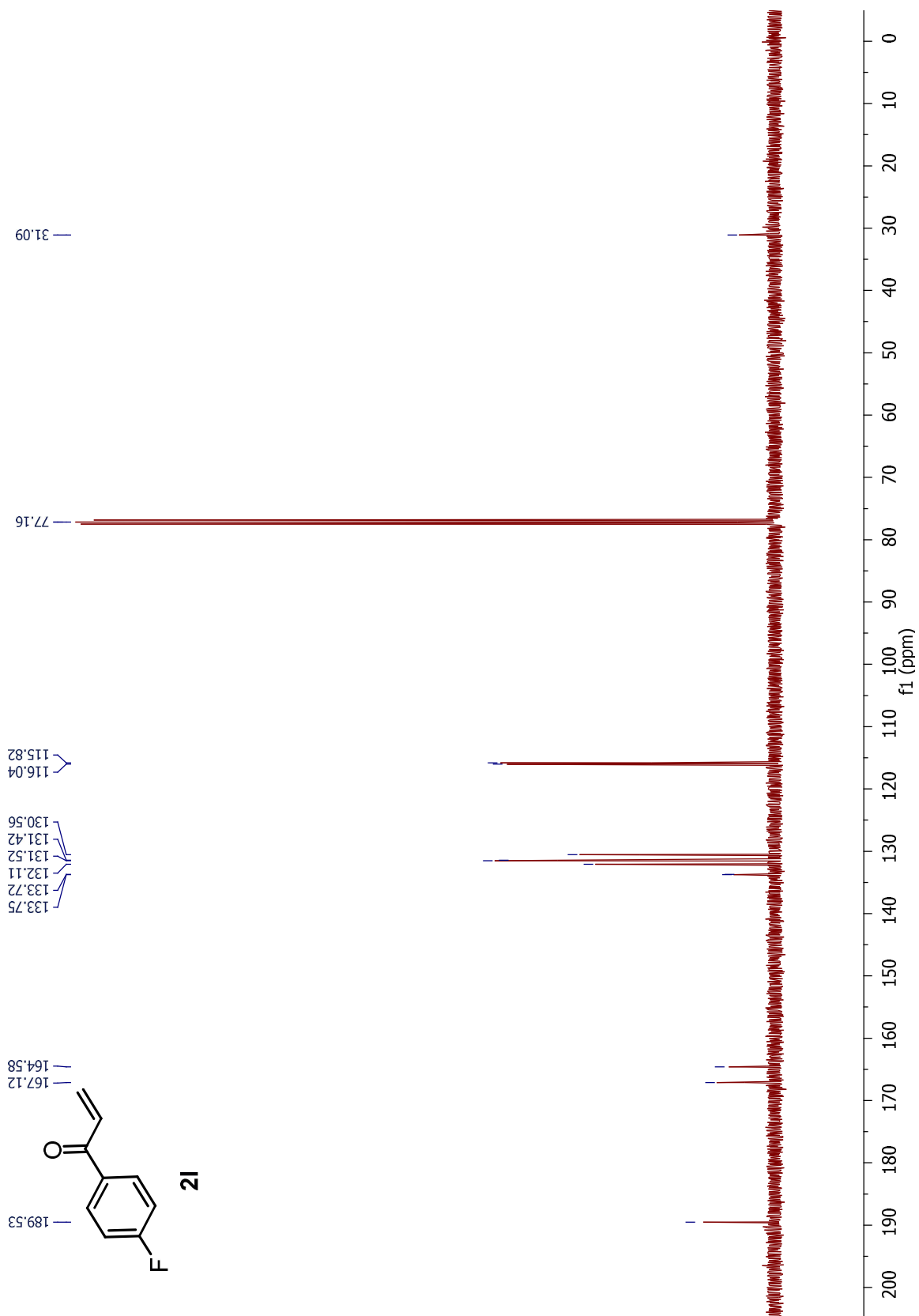


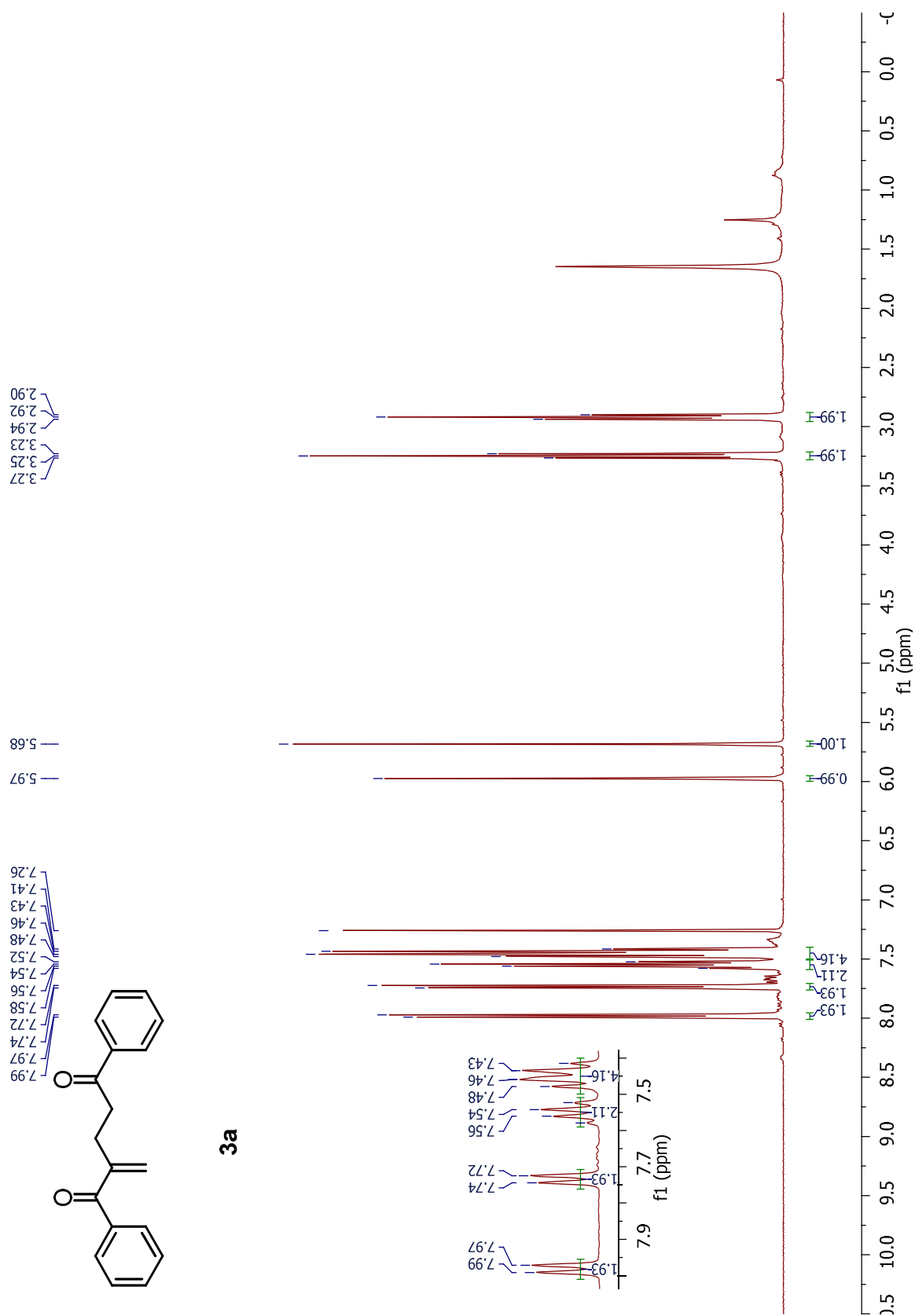


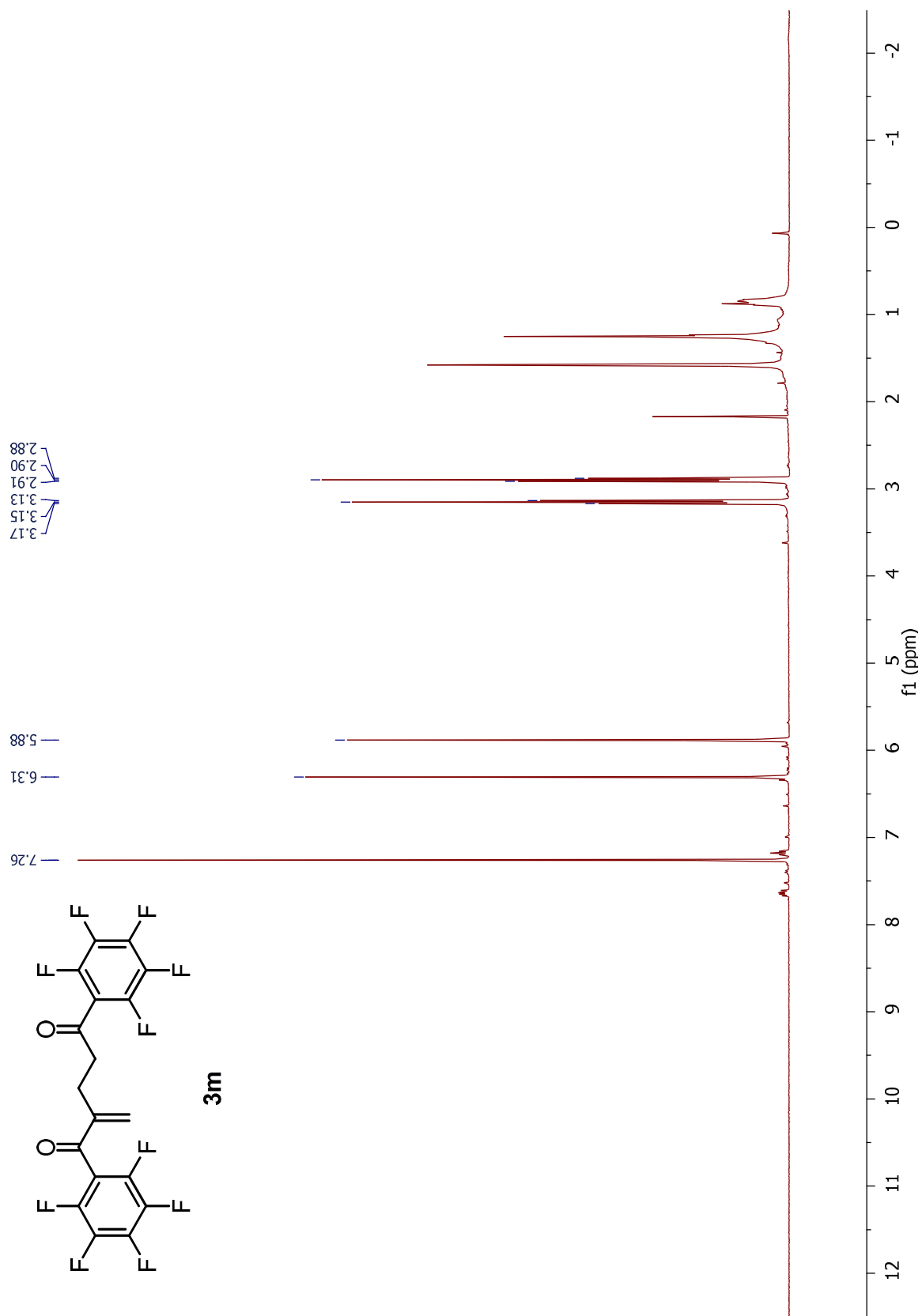
2k











APPENDIX B: ISOMALEIMIDE - NMR SPECTRA

